ENDOSCOPIC INNOVATIONS FOR THE DETECTION AND HAEMOSTASIS OF OESOPHAGEAL CANCER

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Statement of originality

I, Mohamed Hussein, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis

Abstract

Despite advances in endoscopic imaging techniques in the last decade there is still a significant miss rate of early oesophageal cancer in Barrett's oesophagus. Several adjuncts have been developed to support endoscopists with early detection. Artificial intelligence has been shown to play an important role in increased polyp detection during colonoscopies in both pre-clinical studies and randomised control trials with several CE marked technologies now developed to be used real time in endoscopy. Research on the use of Artificial intelligence in Barrett's oesophagus has been more limited and there is a great potential role for it to play in this area.

Early detection of cancer in Barrett's oesophagus is key as patients can then be offered curative endoscopic resection therapy. Also, if not detected early enough advanced oesophageal malignancy can have a poor prognosis. Both these scenarios can also be associated with risks of bleeding which can be managed with several standard endoscopic haemostatic modalities. Treatment options are less favourable for an oesophageal malignancy using standard techniques due to the friable nature of the mucosa. Novel haemostatic powders such as TC-325 have been developed and provide non-contact treatment options for malignancy related bleeding as well as for the treatment of difficult post endoscopic therapy bleeding.

This thesis consists of a literature review around detection and treatment strategies for early cancer in Barrett's oesophagus, and haemostatic treatment options for bleeding following endoscopic therapy in the oesophagus and secondary to advanced oesophageal malignancies. The first three studies have the overarching theme of early detection strategies for Barrett's oesophagus. The first study sets the scene with a retrospective analysis of the accuracy of detection of low-grade dysplasia in Barrett's oesophagus, its natural history and risk factors which help predict the risk of progression to a cancer. The second study shows the development of a novel artificial intelligence algorithms for the detection of dysplasia in Barrett's oesophagus using targeted biopsies on overview images which is compared to the accuracy of non-expert endoscopists. The third study supports the second study where a separate artificial intelligence system is developed for the characterisation of dysplasia on magnification endoscopy which has the added benefit of supporting experts in delineating resection margins for a curative endoscopic resection.

The potential benefits of the second and third studies are to provide adjuncts for earlier detection of cancer which can then be endoscopically resected. There are associated risks of bleeding following a resection. The fourth study in this thesis assesses the outcomes of the treatment of intraprocedural bleeding following endoscopic therapy in the oesophagus with TC-325 haemostatic powder as a monotherapy, part of a combination therapy or as a rescue treatment. Adjuncts like artificial intelligence will be important in minimising an increased miss rate of early cancer leading to advanced oesophageal malignancy which also have an associated complication risk of bleeding. Therefore, the fifth and final study in this thesis assesses the outcomes of the treatment of bleeding advanced oesophageal malignancies with TC-325 as part of a monotherapy, combination therapy or rescue therapy and assesses the impact of this treatment on transfusion requirements. These are commonly difficult to treat, and I assess how TC-325 can bridge this difficulty.

The studies presented in this thesis collectively aim to improve the early detection of cancer in Barrett's oesophagus and improve haemostasis techniques used during endoscopic therapy. Together, these studies contribute to both the diagnostic and therapeutic progress in the endoscopic management of oesophageal disease.

Impact statement

This thesis consists of a suite of five studies all of which have been published in peer reviewed Journals.

The central focus of this thesis is the development of Artificial intelligence (AI) technologies for the detection and characterisation of early cancer in Barrett's oesophagus (Chapters 3 and 4). These formed the basis of two peer-reviewed publications. On the back of this work, I have given oral presentations and prize lectures in the UK, USA and various European conferences. I have received a number of prizes including the inaugural Barrett's oesophagus registry prize awarded at the British Society of Gastroenterology in 2022.

The Artificial intelligence work has formed the basis that contributed to the development of the first CE marked AI device for Barrett's dysplasia detection in the world manufactured by Odin Vision called CADU. This company has now been acquired by Olympus technologies. The device has been successfully used real time on live endoscopy courses broadcast in the United Kingdom and the USA. It has the potential to have an impact on millions of patients' lives around the world.

The retrospective study in chapter 2 was important in showing the scale of the problem of low-grade dysplasia detection which is something artificial intelligence can potentially help support detecting. These patients have a risk of progressing to cancer. The work in this chapter has been published in a peer reviewed journal. I have also delivered a number of conference presentations and prizes including the top abstract award at the United European Gastroenterology week conference in Barcelona.

The work in chapters 5 and 6 formulated part of the TC-325 (Haemospray) registry for Gastrointestinal bleeding. The largest registry of its kind in the world. The work on the management of intraprocedural bleeding and malignancy related bleeding have both been published in peer reviewed journals. I have received prizes for the work including an abstract of distinction and the top abstract prize in the endoscopy section at the British Society of Gastroenterology meeting. As an extension of this work, I have looked at the outcomes of the treatment of peptic ulcer bleeding with TC-325. On the back of this I was invited to present the work on peptic ulcer bleeding in the presidential American Society of Gastrointestinal

Endoscopy plenary session in San Diego awarded to the top abstracts at the digestive disease's week conference. On the back of the work in chapters 5 and 6, I have been invited to give a series of international educational webinars on the use of TC-325 in Gastrointestinal bleeding broadcast around the world. As a culmination of this work, I am currently leading on an international consensus statement involving endoscopists from eight different countries to help define the role of Haemostatic powders in the Gastrointestinal bleed algorithm for endoscopists internationally.

First author peer reviewed publications associated with this thesis

Hussein M*, Lines D, Gonzales-Bueno Puyal J et al.* Computer aided characterization of early cancer in Barrett's esophagus on i-scan magnification imaging: a multicenter international study. Gastrointest Endosc. 2023; 97 (4): 646 -654

Hussein M, *Gonzalez-Bueno Puyal J, Lines D et al.* A new artificial intelligence system successfully detects and localizes early neoplasia in Barrett's esophagus by using convolutional neural networks. United European Gastroenterol J. 2022; 10 (6): 528 – 537.

Hussein M*, Alzoubaidi D, Fraile-lopez M et al*. Hemostatic spray powder TC-325 in the primary endoscopic treatment of peptic ulcer related bleeding: multicentre international registry. Endoscopy. 2021; 53 (1): 36-43.

Hussein M, *Everson M, Haidry R*. Esophageal squamous dysplasia and cancer: Is artificial intelligence our best weapon. Best Pract Res Clin Gastroenterol 2021,52-53: 101723.

Hussein M*, Alzoubaidi D, O'Donnell M et al*. Hemostatic powder TC-325 treatment of malignancy-related upper gastrointestinal bleeds: International registry outcomes. J Gastroenterol Hepatol 2021; 36 (11): 3027-3032.

Hussein M*, Sehgal V, Sami S et al*. The natural history of low-grade dysplasia in Barrett's esophagus and risk factor for progression. JGH open 2021; 5 (9): 1019-1025.

Hussein M*, Gonzalez-bueno Puyal J, Mountney P et al*. Role of artificial intelligence in the diagnosis of oesophageal neoplasia: 2020 an endoscopic odyssey. World J Gastroenterol 2020; 26 (38): 5784-5796.

Hussein M*, Alzoubaidi D, Serna A et al*. Outcomes of Hemospray therapy in the treatment of intraprocedural upper gastrointestinal bleeding post-endoscopic therapy. United European Gastroenterol J. 2020; 8(10): 1155-1162.

Hussein M*, Lovat L, Haidry R.* Advances in diagnostic and therapeutic endoscopy. Medicine 2019; 47 (7): 440-447.

First author oral abstract presentations associated with this thesis

Hussein M, *Puyal JG, Lines D et al*. Deep neural network for the localization of early neoplasia in Barrett's esophagus with targeted biopsies. Gastrointestinal Endoscopy 2021; 93 (6): AB194-AB195. **Oral presentation at Digestive Diseases Week**

Hussein M, *Lines D, Gonzalez-Bueno Puyal J et al*. Computer aided diagnosis network for the characterization of Barrett's dysplasia on magnification i-scan images. UEG Journal 2021; 9 (Supplement 1). **Oral presentation at United European Gastroenterology week.**

Hussein M, *Puyal JG, Brandao P et al*. Deep neural network for the detection of early neoplasia in Barrett's oesophagus. Gut 2021; 70: A17. **Oral presentation at the British Society of Gastroenterology.**

Hussein M, *Puyal JG, Lines D et al.* Deep Neural network for the localisation of early neoplasia in Barrett's oesophagus with targeted biopsies. Endoscopy 2021; 53 (S01): 8-9. **Oral presentation at the European society of Gastrointestinal Endoscopy conference.**

Hussein M, Lines D, Puyal JG et al. **Computer aided diagnosis for the characterisation of dysplasia in Barrett's oesophagus with magnification endoscopy. Endoscopy 2021; 53 (S01): 10. Oral presentation at the European society of Gastrointestinal Endoscopy conference.**

Hussein M, *Alzoubaidi D, O'Donnell et al*. Does Hemospray have a role to play as a combination treatment therapy for upper and lower gastrointestinal bleeds? Outcomes from the Hemospray registry. Gastrointestinal Endoscopy 2021; 93 (6): AB342.

Hussein M, *Alzoubaidi D, de la Serna, A et al*. The role of Hemospray as a monotherapy treatment of upper and lower Gastrointestinal bleeds. UEG Journal 2021; 9 (Supplement 1)

Hussein M, *Alzoubaidi D, de la Serna, A et al*. Change in outcomes over time in patients treated with Hemospray for upper and lower Gastrointestinal bleeds: Outcomes from the Hemospray registry. UEG Journal 2021; 9 (Supplement 1)

Hussein M, *Sehgal V, Magee C et al.* The natural history of low-grade dysplasia in patients with Barrett's oesophagus: a tertiary centre experience. UEG journal 2019; 7 (8). **Recognized as a *poster of excellence* and presented as an oral presentation in the 'posters in the spotlight' session at United European Gastroenterology week. It received the top prize for that session.**

Hussein M, *Alzoubaidi D, Graham D et al*. Outcomes on the use of hemospray in upper gastrointestinal bleeds secondary to tumours: Outcomes from the multicentre international Hemospray registry. UEG Journal 2019; 7(8). **Oral presentation at United European Gastroenterology week.**

Hussein M, *Alzoubaidi D, Fraile JM et al.* Outcomes on the use of Hemospray in gastrointestinal bleeds secondary to peptic ulcer bleeds: Outcomes from the multicentre international Hemospray registry. Gastrointestinal Endoscopy 2019; 89 (6). **International oral presentations in San Diego '19 in the American society of GI endoscopy presidential plenary session as one of the top scoring abstracts in the Digestive Diseases Week conference and a second oral presentation in the topic forum session**

Prizes received associated with this thesis

The following prizes were received in relation to the research on Artificial intelligence and Barrett's oesophagus (Chapters 3 and 4 of this thesis):

- Invited Prize lecture given at the British Society of Gastroenterology conference (June 2023) for receiving the Barrett's oesophagus registry prize the previous year
- I received the first national Barrett's oesophagus Registry Prize awarded by the British society of Gastroenterology in June 2022
- Nominated for the young talent award, EndoSwiss 2021
- Article of the month in the Gastrointestinal Endoscopy journal – in relation to the following paper:

  Hussein M, Lines D, Gonzales-Bueno Puyal J et al. Computer aided characterization of early cancer in Barrett's esophagus on i-scan magnification imaging – Multicenter international study. Gastrointestinal Endoscopy (2022), doi: https:// doi.org/10.1016/j.gie.2022.11.020
- Received a poster of distinction at Digestive diseases week conference (USA, 2021) for the following abstract:

  'Computer aided diagnosis for the characterisation of dysplasia in Barrett's esophagus with magnification endoscopy'

The following prizes were received in relation to the research on the natural history and risk factors for progression of low-grade dysplasia (Chapter 2 of this thesis):

- Recognised as poster of excellence at United European Gastroenterology conference 2019
- Received the top abstract award at the United European Gastroenterology Conference 2019 in that session
- Received a 750 Euro travel grant for United European Gastroenterology week (2019)

The following prizes were received in relation to the research work on TC-325 (Haemospray) and Gastrointestinal bleeding (chapters 5 and 6 of this thesis)

- Abstract of distinction in the British Society of Gastroenterology (2021) received for the following abstract:
  'Hemospray in the treatment of non-variceal upper Gastrointestinal bleeds: Outcomes from the first 500 patients in the registry'

- Received top prize in the endoscopy section of the British Society of Gastroenterology conference (2019). The abstract was also accepted as an abstract of distinction. This was for the following abstract:

  'Outcomes on the use of Hemospray in gastrointestinal bleeds secondary to tumours: Outcomes from the multicentre international Hemospray registry'

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David Lines and Juana Gonzales-Bueno Puyal (Odin vision/UCL) developed the convolutional neural network architectures used in the experiments in chapter 3 and 4 of this thesis and provided reports of performance metrics. Daniel Toth (Odin vision/UCL) developed the computer annotation tool used to annotate the videos and images in chapter 3 and 4 in this thesis.

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I would like to express my deepest gratitude to my supervisors Dr Rehan Haidry and Professor Laurence Lovat for all their guidance and support throughout this journey. Dr Haidry's passion and drive for endoscopic innovation have been a source of inspiration to me. He has been a mentor to me endoscopically and for that I will be forever grateful. Professor Lovat's enthusiasm and energy for research has influenced and shaped my approach to academic work. I won't forget the time he gave to listen to me practice multiple times for my first USA (DDW) oral presentation!

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Abbreviations used

AI	-	Artificial intelligence
APC	-	Argon plasma coagulation
ASGE	-	American Society of Gastrointestinal Endoscopy
ACG	-	American College of Gastroenterology
AUC	-	Area under the curve
BLI	-	Blue light imaging
BO	-	Barrett's oesophagus
BSG	-	British Society of Gastroenterology
CLE	-	Confocal laser endomicroscopy
CNN	-	Convolutional neural network
CPU	-	Central processing unit
EMR	-	Endoscopic mucosal resection
ESD	-	Endoscopic submucosal dissection
ESGE	-	European Society of Gastrointestinal Endoscopy
FP	-	False positive
FPS	-	Frames per second
FN	-	False negative
GI	-	Gastrointestinal
GORD	-	Gastro-oesophageal reflux disease
GPU	-	Graphics processing unit
HD	-	High definition
HGD	-	High grade dysplasia
IMC	-	Intramucosal adenocarcinoma
IND	-	Indefinite for dysplasia
LGD	-	low grade dysplasia
NDBO	-	Non dysplastic Barrett's oesophagus
NSAID		Nonsteroidal anti-inflammatory drug
OAC	-	Oesophageal adenocarcinoma
OGD	-	Oesophago-gastro-doudenoscopy
OE	-	Optical enhancement
PPI	-	Proton pump inhibitor
RFA	-	Radiofrequency ablation

TFF3 - Trefoil factor 3 markers

TP - True positive

UGIB - Upper Gastrointestinal bleed

VLE - Volumetric laser endomicroscopy

$WATS^{3D}$ Wide-area transepithelial sampling with a 3-dimensional computer assisted analysis

WL - White light

CHAPTER 1

INTRODUCTION

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1.1 Barrett's oesophagus

1.1.1 History of Barrett's oesophagus

Barrett's oesophagus (BO) was named after a surgeon in London, Norman Rupert Barrett, who described patients with a distal ulceration in the oesophagus lined by columnar epithelium (1). He argued that this portion was a tubular segment of the stomach which was tethered into the chest by a congenitally short oesophagus. In 1953 Allison and Johnstone refuted Barrett's claims that this columnar-lined viscus was the stomach and suggested that it should be called lower oesophagus lined by columnar epithelium(2). They also linked the association between Gastro-oesophageal reflux disease (GORD) and columnar lined oesophagus. Bosher and Taylor in 1951 were the first to describe intestinal-type goblet cells in the columnar lined oesophagus which we now know as intestinal metaplasia(3). By the late 1980s it became well established that Barrett's oesophagus was associated with adenocarcinoma. Intestinal metaplasia was accepted as the most common type of Barrett's epithelium and also the type associated with the development of cancer(4)(5).

1.1.2 Definition and diagnosing Barrett's oesophagus

Barrett's oesophagus occurs when the normal squamous epithelium in the distal oesophagus transforms into columnar lined intestinal type cells. This transition is defined as intestinal metaplasia and normally occurs when the oesophagus is continuously exposed to gastric acid therefore contributing to inflammation of the distal oesophageal mucosa proximal to the gastro-oesophageal junction (GOJ) (6)(Figure 1).

The published British Society of Gastroenterology (BSG) guidelines have defined Barrett's oesophagus *'as an oesophagus in which any portion of the normal distal squamous epithelium lining has been replaced by metaplastic columnar epithelium which is clearly visible endoscopically (≥ 1cm) above the GOJ and confirmed histopathologically from oesophageal biopsies'*.(7)

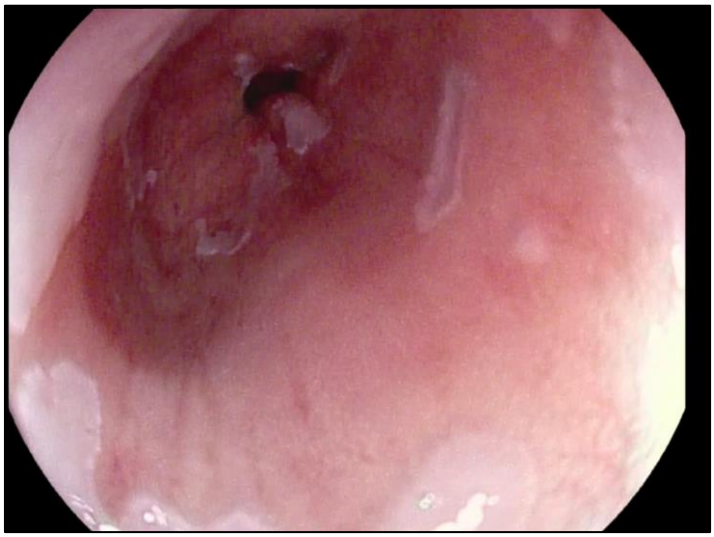


Figure 1 Endoscopic assessment of Barrett's oesophagus

Both the BSG and American College of Gastroenterology (ACG) guidelines are in agreement that at least 1cm of columnar mucosa is required for a diagnosis of BO. All patients with an irregular z-line (< 1cm from the top of the gastric fold) and in the absence of any visible lesions should not undergo biopsies(7)(8).

1.1.3 Epidemiology

1.1.3.1 Prevalence and incidence of Barrett's oesophagus

Due to the asymptomatic nature of BO it is difficult to give a clear estimate of the population prevalence of this condition (9). It is found in 10-15% of patients presenting to the Gastroenterology clinic with a history of GORD (10). Based on previous western population-based studies it is estimated to be present in approximately 1-2% of the population (11). This patient cohort has a 10-55 fold higher risk of developing oesophageal adenocarcinoma (OAC) (12). The incidence of BO detected during endoscopy has increased significantly over the last 30 years which could in part be related to increased endoscopies during this period. Data has shown incidence increasing from 14.3/100,000 persons to 23.1/100,000 persons between 1997 and 2002. These increases are partially related to the increasing availability of endoscopy over the last three decades (13)(14).

1.1.3.2 Age, sex and ethnic variation

Caucasian males have a greater predisposition to the development of BO. On average it is often diagnosed in the 6th or 7th decade of life(13) (15). There is evidence males develop BO earlier

than females. Overall, BO cases are more common in men with a ratio of 2:1 in favour of males, and in younger adults the ratio is 4:1 favouring men(15).

In a large cross-sectional study in the United Kingdom (UK) it was found that Caucasians had significantly higher prevalence of BO compared to the Afro-Caribbean or Asian population (16). Some studies have shown variation in the prevalence of BO in ethnic groups living in the same country suggesting that there may potentially be other polygenetic factors contributing to this variation in prevalence.

There are a number of environmental factors that have a strong association with BO. Certain factors are more common in developed countries such as GORD, hiatus hernia and obesity. Genetic factors also potentially play a very important role(13).

1.1.4 Risk factors for the development of Barrett's oesophagus

1.1.4.1 Gastro-oesophageal reflux disease

GORD is the main risk factor associated with the development of BO. This cohort is 6-8 times more likely to develop BO. The risk of developing BO increases with increasing severity and duration of GORD symptoms.

Studies have shown that patients with BO have more significant and longer episodes of acid exposure, lower PH, reduced baseline lower oesophageal sphincter tone and weaker peristaltic contractions when compared to patients without evidence of BO (17) (18).

It is not quite clear what impact proton pump inhibitors have on the development of BO. The relationship between those with reflux and BO is not completely explained by GORD. Obesity may be a mediating factor contributing to this. It can predispose to the development of a hiatus hernia which in turn contributes to increased GORD symptoms and relaxation of the lower oesophageal sphincter.

1.1.4.2 Obesity

The significant rise in BO and OAC has been concurrent with an increase in the incidence of obesity in the west. The prevalence of obesity has gone up from 25% in the 1970's to 35% more

recently. A meta-analysis study has shown an increased risk of BO associated with a body mass index (BMI) greater than 30kg/m^2(19). Overall patients with BO have been shown in studies to have a higher BMI than people without BO(20).

Some studies have shown that the central obesity rather than BMI is associated with the risk of development of BO. A pooled analysis showed that waist circumference increases the risk for both females (Odds ratio 3.75) and males (odds ratio 2.24).(21)

1.1.4.3 Alcohol

There have been variable results with regards to the association between alcohol intake and the development of BO. The BEACON consortium pooled data from 5 studies assessing the risk of BO with alcohol use(22). Drinking between 3 to 5 drinks per day was associated with a statistically significant reduction in the risk of development of BO (Odds ratio 0.57)(22). Wine consumption has been found to be associated with an inverse risk of BO (Odds ratio 0.71)(13).

The evidence is overall unclear with regards to the association between these two factors and clearly more data and studies are needed.

1.1.4.4 Smoking

Most studies have found an association between smoking and the risk of developing BO. A pooled analysis of 5 case-control studies found that the risk of BO increased consistently with the number of pack years(23). There was evidence of an increased risk of developing BO with both GORD and smoking versus smoking alone.

1.1.4.5 Helicobacter pylori

Helicobacter pylori has a strong association with intestinal metaplasia in the antrum and body of the stomach. It is a known risk factor associated with peptic ulcer disease, chronic gastritis and gastric cancer. Studies have shown that Helicobacter pylori may be inversely related to the development of BO. This may be due the reduced acid production in the stomach. Different strains may have different abilities in contributing to BO risk(24).

1.1.4.6 Family history

The prevalence of BO in individuals with a family history of BO is estimated to be 6 – 7.3%. (25) Such studies should be interpreted with caution as there may be environmental factors such as diet and smoking contributing to this. There may also be a degree of detection bias in family members as there will be increased chance of having an endoscopy in this group compared to the general population (26).

1.1.4.7 Medication

Studies have shown that medications such proton pump inhibitors and statins may be associated with a decreased risk of developing BO(26).

1.1.4.8 Other risk factors

Obstructive sleep apnoea and metabolic syndrome appear to increase the risk of BO. A study found that after controlling for obesity and GORD, obstructive sleep apnoea was associated with an elevated risk of BO (OR 1.8)(27). It is believed this increased risk might be associated with increased levels of cytokines and adipokines in these patients(28).

Low birth weight has been identified as a potential risk factor. A Swedish study showed that prematurity is associated with an increased risk of oesophagitis which is most significant in those small for gestational age(29). Follow up research by this group showed that the risk of BO was significantly increased in those with the lowest birth weights (OR 8.2)(30).

Table 1 summarises the main risk factors associated with BO and its progression.

1.1.4.9 Risk factors for progression of Barrett's oesophagus to Oesophageal adenocarcinoma

Many of the risk factors associated with the development of BO are also associated with the risk of progression from BO to OAC. Caucasian ethnicity, male sex, increased age and the increased length of BO are associated with a significant risk of progression. Studies have shown that in nondysplastic BO the risk of developing dysplasia increases by approximately 3.3% per year of age. GORD, smoking and BMI/central obesity are also associated with an increased progression risk(31)(32)(33). The presence of dysplasia in BO is a significant risk factor for progression to BO. (26)

Table 1:Risk factors for development of Barrett's oesophagus and its progression to high grade dysplasia/OAC(34)

Risk factor	Risk factor for developing BO	Risk factor for progression of BO to HGD/OAC	Risk factor for recurrence of BO after endoscopic treatment
Male	X	X	
Increased age	X	X	X
GORD	X		X
Smoking	X	X	
Central obesity	X		
Family history of BO	X		
Caucasian	X		
Size of hiatus hernia	X		X
Confirmed/persistent Low-grade dysplasia		X	
High grade dysplasia/OAC		X	X
Longer segment of BO		X	X

BO = Barrett's oesophagus; OAC = oesophageal adenocarcinoma; HGD = high grade dysplasia

1.1.5 Barrett's oesophagus to oesophageal adenocarcinoma sequence

BO is the only known precursor of OAC. There is a sequential progression starting from normal BO with columnar intestinal metaplasia, to dysplasia and to invasive cancer (Figure 2).

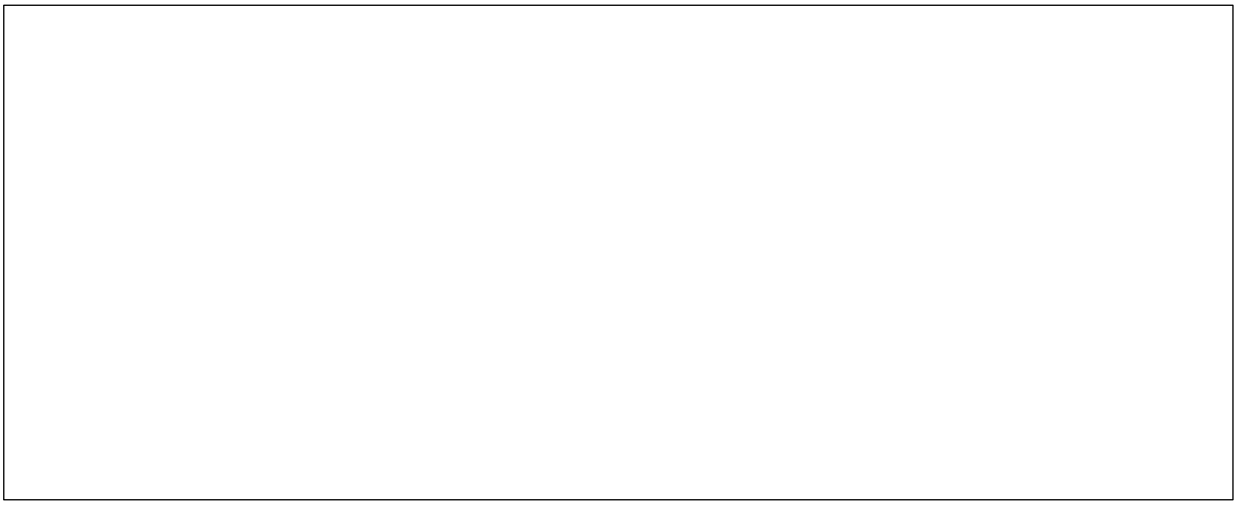


Figure 2: Injury of the oesophagus secondary to reflux may lead to BO. In BO normal squamous epithelium is replaced by columnar epithelium (intestinal metaplasia). BO is premalignant and may progress to dysplasia and in turn oesophageal adenocarcinoma. Image courtesy of Peters et al. (26)

Initially non dysplastic BO (NDBO) progresses to low grade dysplasia (LGD) and then to high grade dysplasia (HGD) and then progresses to an invasive cancer. The rate of progression from NDBO to OAC varies from 0.2% to 0.5% per year, and from LGD to HGD/OAC varies between 0.4% and 13.4% (34). The higher rates of progression with LGD were found in patients whose diagnosis was confirmed after review by an expert histopathologist and in patients with persistent LGD in a sequence of endoscopies (35) (36) (37). The rate of progression from HGD to OAC varies between 5% and 8% per year (38) (39).

Advances in endoscopic therapy over the last 20 years has allowed for endoscopic intervention to occur in the dysplastic stage of the sequence therefore minimising progression to oesophageal adenocarcinoma and preventing the need for an oesophagectomy which has associated risks (40).

1.1.5.1 Non dysplastic Barrett's oesophagus

This consists of intestinal metaplasia without any features that are suggestive of dysplasia. A Danish cohort study evaluated 11000 BO patients. The incidence of adenocarcinoma in non-dysplastic BO was 1 case per 1000 person years over a median follow up time of 5.2 years(41). A cohort study from Ireland showed a progression rate of 0.17% per year(42)(43). A population-based study from a Dutch nationwide registry of 12,728 non dysplastic BO patients showed that patients with stable non dysplastic BO had a low risk of progression. The authors made an argument for potentially extending surveillance intervals for patients with persistent non dysplastic BO(44).

1.1.5.2 Low grade dysplasia

The histological criteria for LGD in BO include crypts with preserved architecture or minimal distortion, and atypical pencil-shaped nuclei mainly limited to the basal portion of the cell cytoplasm. The nuclei are normally elongated, hyperchromatic and crowded(45).

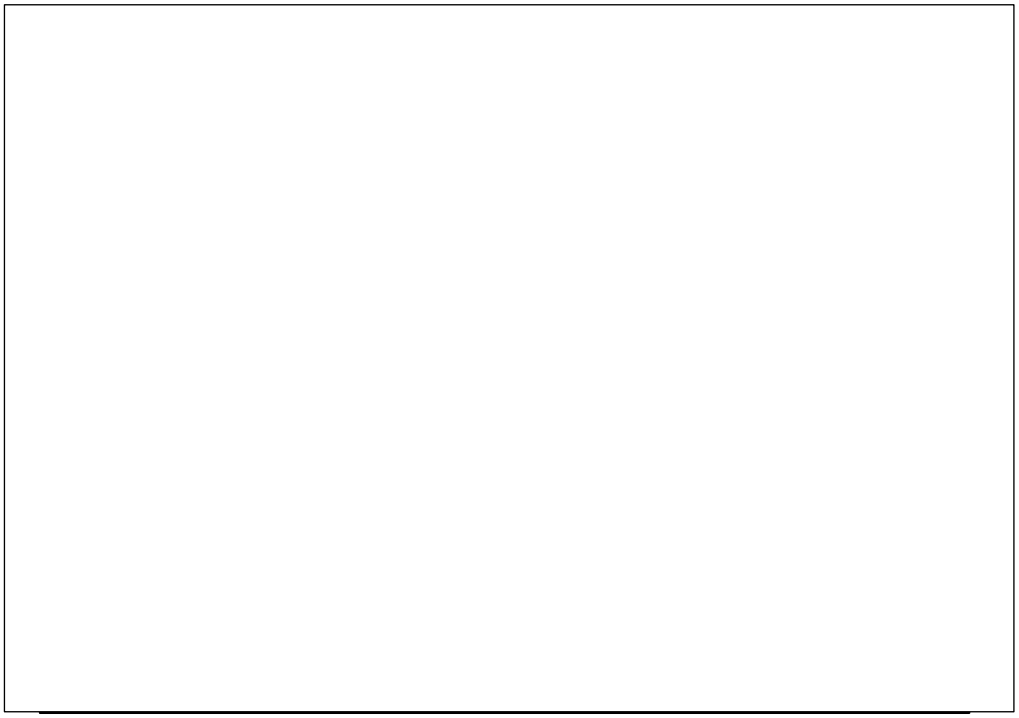


Figure 3 Medium power (A) and high power (B) view of low-grade dysplasia in Barrett's oesophagus (45)

There is variability in the diagnosis of LGD in BO. Patients can be downstaged to non-dysplastic Barrett's oesophagus (NDBO) or indefinite for dysplasia or upstaged to high grade dysplasia (HGD) when reviewed by expert pathologists. All patients with an initial diagnosis of LGD should be treated with a high dose proton pump inhibitor followed by a repeat assessment in 6 months. This is to reduce the likelihood of a false positive due to inflammation. A study showed that 32% of patients that developed incidental LGD in BO had intermittent LGD fluctuating between NDBO and LGD in BO. If a repeat diagnosis of LGD is confirmed, then these patients are offered endoscopic eradication therapy(46).

There is not enough data with regards to the recurrence of disease following endoscopic therapy. Following complete eradication of LGD there should be a surveillance endoscopic assessment

at 6 months and then annually thereafter(46). This is a longer interval than following treatment of HGD or intramucosal cancer.

Federici et al evaluated the cost effectiveness of radiofrequency ablation treatment of BO. They found that radiofrequency ablation treatment for LGD in BO was effective and more costly than active surveillance(47).

There is variability in the data with regards to the progression risk of LGD in BO and risk factors for progression. A retrospective study on 1579 patients with LGD in BO showed there was a higher risk of progression in patients with confirmed and persistent LGD. The incidence of HGD and/or oesophageal cancer in patients with persistent LGD was 7.65/100 person-years (95% CI, 4.45-12.34), and in patients without persistent LGD this was 2.32/100 person-years (95% CI, 1.08-4.40/100 person-years)(48). A randomised study showed a high risk of progression of LGD in BO. 26.5% progressed to HGD/oesophageal cancer in the surveillance cohort of patients versus 1.5% in the cohort treated with ablation(49).

1.1.6 Diagnostic biopsy protocol for Barrett's oesophagus – Seattle Protocol

As per the ACG and BSG the diagnosis of BO is when there is evidence of columnar lined mucosa ≥ 1cm proximal to the gastro-oesophageal junction with histological confirmation of intestinal metaplasia containing goblet cells(34).

BO is classified as short segment if the length of BO is less than 3cm. It is classified as long length if greater than or equal to 3cm. The reporting of BO is standardised using the Prague classification system(34). This describes the circumferential extent (C) and maximal extent (M) of BO using the landmarks of the Gastro-oesophageal junction and the squamocolumnar junction (Figure 3).

The BSG recommendation is that endoscopic reporting following assessment of BO should be done with a minimum dataset which includes the length using the Prague criteria and any islands above the main columnar BO segment(7).

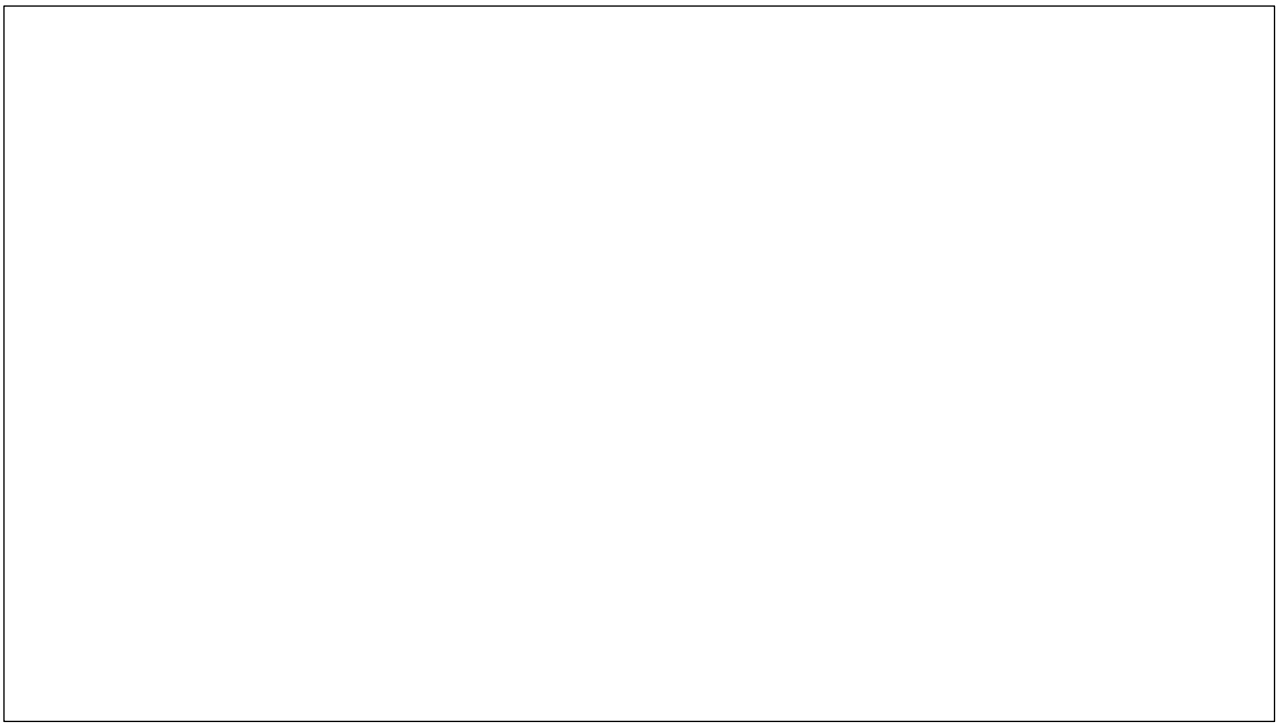


Figure 4: Image illustrating Prague classification for Barrett's oesophagus. C = circumferential extent of Barrett's. M = maximal extent of Barrett's. This is an example of a C2M5 Barrett's oesophagus. Image courtesy of Sharma et al(50)

During surveillance endoscopy for assessment of BO biopsies are taken as per the Seattle protocol. This involves quadrantic biopsies every 2cm of BO. In addition to this any visible lesions are target biopsied.

Any visible lesions should be targeted first. Following this Seattle protocol biopsies should be taken starting at the most distal end of the BO segment and advancing more proximally to avoid the obscuring of views from bleeding secondary to the biopsies(7).

1.1.7 Screening for Barrett's oesophagus

1.1.7.1 Endoscopy and biopsy

An endoscopy is the gold standard method for detecting BO. However, this method is invasive, expensive and with associated risks which do not make it an ideal candidate for a widespread BO screening programme(51).

Patients are selected for endoscopic screening based on their higher risk of developing BO than the rest of the population. The endoscopy is performed via the oral route and normally with sedation. The procedure is performed with a high-definition endoscope in combination with

acetic acid or chromendoscopic imaging to identify areas of intestinal metaplasia and dysplasia. The results of the endoscopy and biopsy help risk stratify patients to determine the interval surveillance approach and further management(52).

The endoscopic approach and biopsies has a high accuracy for the diagnosis of BO however it is associated with the limitation of high costs. There is no evidence that an endoscopy is cost effective for screening an unselected population for BO or oesophageal adenocarcinoma(53).

1.1.7.2 Standard endoscopy with cytological analysis

Brush cytology sampling of the oesophageal mucosa can be performed during an endoscopic procedure. This would potentially allow larger areas of the oesophagus to be sampled. Saad et al evaluated 327 consecutive paired brushing and oesophageal biopsies during the same endoscopic procedure. They have shown that cytology brushes which compliments standard histology has a high accuracy for the diagnosis of HGD and OAC with a sensitivity of 90%, and a moderate degree of sensitivity for BO versus histological analysis (60% versus 92%) and a low sensitivity for LGD compared to analysis with histology (20% versus 97%)(54). There can be false positive results due to the presence of acute inflammation in the oesophagus. There is an argument that the added cost outweighs the benefit from adding the cytology brush to current histological analysis methods(51).

Wide area transepithelial sampling with a 3-dimensional computer assisted analysis ($WATS^{3D}$) is used for sampling of the oesophagus. This uses a brush to sample a large area of the oesophagus. Samples are then analysed using a computerised microscopy. This creates a 3D image of the tissue and localises areas of dysplasia, adenocarcinoma, and intestinal metaplasia. They are reviewed by an expert histopathologist to confirm the diagnosis. A study has shown that $WATS^{3D}$ identified 21 cases of BO which were missed by a forceps biopsy. It also found that using the $WATS^{3D}$ brush in addition to standard biopsies increases the yield of BO during surveillance endoscopy(55). Trindade et al showed that when WATS-3D is added as an adjunct to biopsies it increases the diagnostic yield of both BO and BO-associated dysplasia in patients with both long and short segment BO. However, ESGE guidelines do not recommend the use of WATS-3D as an alternative, or adjunct to biopsy forceps during BO surveillance. This is due to the uncertainty with regards to the interpretation of dysplasia picked up by the brush, and also uncertainty with regards to the cost effectiveness of incorporating brush sampling into BO surveillance(56).

1.1.7.3 Transnasal endoscopy

Transnasal endoscopy is considered an effective alternative to standard per oral gastroscopy for detecting and screening for BO. It is normally performed without sedation using an ultrathin endoscope via the nasal route. It is performed with the patient sitting up.

Studies have shown that it has a sensitivity of 98% for the detection of columnar lined oesophagus and 91% for the detection of intestinal metaplasia. They showed a specificity of 100% when compared to a standard gastroscopy(57).

Transnasal endoscopy is well tolerated and can often be done in the outpatient clinic setting which also maximises capacity on the endoscopy unit. It minimises stimulation of the gag reflex. Not requiring sedation helps with cost saving due to less equipment, monitoring and nursing work force for the during and after the procedure (58). It is becoming an important screening strategy for diagnosis of early oesophageal cancer and BO. It is an endoscopic modality that can potentially help support clearance of the backlog in gastroscopies present since the Covid-19 pandemic(59).

Advances in endoscopic technology also mean that transnasal endoscopy offers comparative optical performance to a standard gastroscopy therefore maximising early cancer detection. A study showed that over 90% of patients describe no discomfort following this procedure and those who had previously had a standard per oral gastroscopy had preferred the nasal approach. All biopsies were determined to be sufficient to reach an appropriate diagnosis(58).

1.1.7.4 Cytosponge

This is a non-invasive technology for the detection of BO and associated dysplasia. This consists of reticulated foam which is approximately 30mm in diameter compressed inside a gelatin capsule and attached to a string. It is swallowed by a patient and then retrieved by the operator using the string after approximately 5 minutes. Cells from the oesophagus are absorbed by the sponge. These cells are then retrieved, and immunohistochemistry is performed to detect the expression of specific markers. The trefoil factor 3 markers (TFF3) can distinguish intestinal metaplasia cells in BO from columnar cells from gastric cardia(60).

A multicentre randomised controlled trial showed that in patients with gastro-oesophageal reflux that are offered cytosponge TFF3 testing there is an increased detection of BO and this could lead to the detection of early cancer(61).

A retrospective multicentre cross-sectional study showed that cytosponge atypia, P53 over expression in combination with clinical risk factors for progression can be used to prioritise which patients require an endoscopy. This can potentially be a method to reduce the endoscopic workload(62).

A pilot study with cytosponge was performed on patients with reflux and under BO surveillance in 61 hospitals in the UK. Cytosponge biomarker tests allowed for better targeting of endoscopy for higher risk individuals. The authors also concluded that those with ultra short Barrett's segment and TFF3 negative should have their requirements for further Barrett's surveillance reconsidered and discharge should be considered(63).

1.1.7.5 Capsule endoscopy

Oesophageal capsule endoscopy is a minimally invasive way of visualising the upper Gastrointestinal (GI) tract. It has advantages compared to a standard endoscopy in that no sedation is required and it is better tolerated. The movement and positioning of the video capsule relies on the movement and peristalsis of the upper GI tract. This can have a potentially negative impact on capturing sufficient images. There is an added challenge in the stomach due to its large capacity. There may be difficulty in assessing the cardia and fundus which would normally require manual endoscopic manoeuvring to be able to sufficiently assess these areas(64).

Peristalsis powered oesophageal video capsules have been shown in a metanalysis of nine studies to have a reasonable sensitivity of 77% and specificity of 86% for diagnosing BO. However in comparison to an Oesophago-gastro-doudenoscopy (OGD) that would remain the gold standard(65). Most studies favour a standard OGD in comparison to oesophageal video capsule endoscopy to diagnose BO(64).

A string capsule endoscopy was used to screen for BO in 100 patients with symptoms of reflux. BO was detected with a sensitivity and specificity of 78% and 83% respectively(66).

A cost benefit analysis comparing standard endoscopy with capsule endoscopy found a standard endoscopy to be more cost effective for screening patients with symptoms of reflux. This is due to the higher prevalence of BO in this cohort of patients(67). It needs to be kept in mind that tissue samples cannot be taken during a capsule endoscopy and therefore patients with BO will end up requiring a second procedure(60).

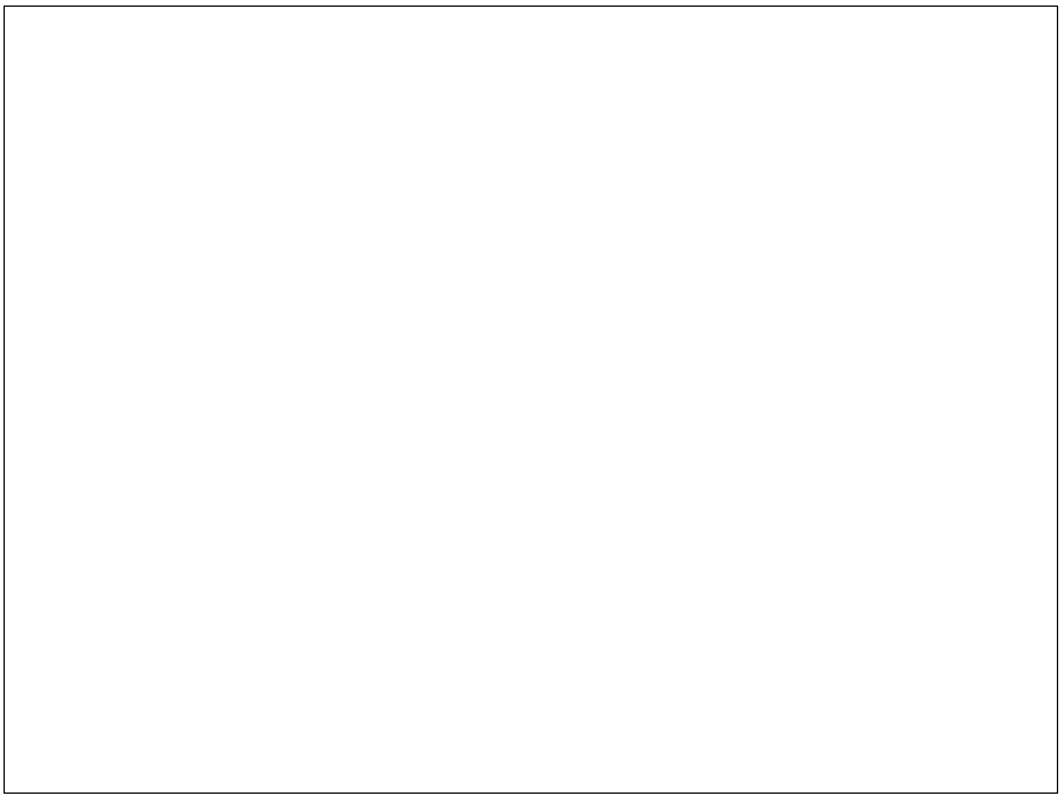


Figure 5: Potential screening tools for Barrett's oesophagus. (A) WATS3D brush (68)*, (B) capsule endoscopy* (69)*, (C) Cytosponge* (70)*.*

1.1.8 Biomarkers for Barrett's oesophagus

A number of biomarkers have been studied for the diagnosis of BO.

Trefoil factor 3 (TFF3) is a protein which is expressed from the columnar surface layer of the stomach and also the intestines. It promotes mucus secretion and also supports the acceleration of healing from mucosal injury(71). A study showed that it was significantly more upregulated in BO compared to normal oesophagus ($P<0.01$)(72). It showed that this was a promising potential biomarker for screening for BO as it expressed it on the BO surface layer but not in adjacent tissue types.

MiRNAs are also promising biomarkers. A study found that the hypermethylation of TFPI2, TWIST1, ZNF345 and ZNF569 genes was found in the BO biopsies compared with squamous mucosa and gastric cardia biopsies ($p<0.05$). Following testing in cytosponge samples these 4 genes were hypermethylated in patients with BO when compared to patients with symptoms of reflux ($p<0.001$). The optimal biomarker identified was TFPI2 which detected BO with a sensitivity of 82.2% and specificity of 95.7%(73).

Being able to predict which patients with BO are most likely to progress to a cancer is important particularly with regards to risk stratifying patients, offering therapeutic treatment options and determining surveillance intervals. Biomarkers that can potentially predict the risk of progression of BO have been studied(71).

P53 protein is an important predictor of the risk of progression of BO. It is recommended in societal guidelines as a risk stratification tool for prediction of progression(74).

1.1.8.1 Role of P53 in the assessment of dysplasia in Barrett's oesophagus

P53 is a tumour suppressor protein which is often mutated in BO. The overexpression of P53 is detected by immunohistochemistry(75).

There is a current problem with interobserver variation in the grading of dysplasia in BO including amongst experts. Due to random sampling on endoscopy areas of dysplasia can be missed during surveillance assessments. Therefore, there is a concern with regards to over or under diagnosis of dysplasia. Therefore, biomarkers like P53 could potentially improve the risk stratification of these patients and standardise assessments(75). Several studies have shown that P53 improves the interobserver agreement between histopathologists in the diagnosis of low-grade dysplasia, high grade dysplasia and adenocarcinoma in BO compared to histopathology assessment alone.

Studies have shown that P53 over expression has a potential role in risk stratifying the risk of progression to HGD and OAC. Neyaz et al developed criteria to define P53 over expression. They found that 39% of non-dysplastic patients that progressed met these criteria, and only 7% of patients that did not progress met these criteria(76). Kastelein et al showed that a quarter of patients diagnosed with an abnormal P53 expression developed HGD or OAC. Abnormal P53

expression was found in 37% of non-dysplastic biopsies. 78% of LGD biopsies and all HGD/OAC biopsies contained aberrant P53(77). Nowden et al show that P53 immunohistochemistry is strongly associated with neoplastic progression regardless of the baseline histological diagnosis (NDBO, indefinite for dysplasia, LGD)(74).

Based on these as well as several other studies P53 immunohistochemistry has the potential in predicting neoplastic progression from NDBO/indefinite for dysplasia and LGD to HGD. In addition to being a potential predictive marker P53 immunohistochemistry has been also shown to support the histological diagnosis of dysplasia.

Tomaszeski et al used reproducible criteria for defining aberrant P53 expression. They showed that a single strongly p53-positive gland can distinguish dysplasia with a sensitivity of 98.6%(78). Januszewicz et al showed with the inclusion of P53 immunohistochemistry there was a more than 40% reduction in the diagnosis of indefinite for dysplasia in Barrett's oesophagus, therefore reclassifying it to definitive dysplasia(79).

Overall, P53 is an important tool and adjunct that potentially increases diagnostic confidence and reproducibility of dysplasia in BO. It helps improve the interobserver agreement amongst pathologists. It also would potentially help in determining risk of progression. Standardisation of the analysis of P53 is a challenge which has limited its widespread adoption in clinical practice. Optimal interpretation strategies would need to be validated in prospective clinical studies(75).

1.1.9 Surveillance for Barrett's oesophagus

The timing of surveillance of Barrett's oesophagus is determined by the grade of dysplasia and the length of the BO segment. In the United Kingdom if the biopsies show non dysplastic BO, and the length of the Barrett's segment is less than 3cm, Patients will have a repeat surveillance endoscopy in 3-5 years. If the length of the BO segment is more than 3cm, patients will be offered a surveillance endoscopy in 2-3 years (Figure 6)(7).

If biopsies show LGD patients will be offered a repeat endoscopy in 6 months. If LGD is confirmed on the second endoscopy ablation treatment is offered to patients. If intervention is declined, then 6 monthly surveillance endoscopies are offered(7).

If biopsies show HGD. Patients are referred to a tertiary referral centre for endoscopic resection of any visible lesions or Radiofrequency ablation if no visible lesions in the Barrett's segment(7).

1.1.9.1 The challenges of endoscopic surveillance of Barrett's oesophagus

The distribution of dysplasia in BO can be patchy or in very small and isolated areas surrounded by large areas of non-dysplastic BO. Therefore, even with full compliance with Seattle protocol biopsies only 5-10% of the BO mucosa is sampled leaving large areas unsampled and therefore dysplasia can be missed (80).

There is poor adherence to the Seattle protocol of four quadrantic biopsies every 2cm of BO. A study found that there was a 51.2% adherence to the Seattle protocol which decreased with an increased length of BO, leading to a reduced dysplasia detection rate (80)(81).

Most dysplasia or early neoplasia in BO is very subtle and therefore it can be a challenge for an endoscopist to identify. This can be more difficult with saliva, food debris and mucus obscuring the mucosa along with the oesophageal motility. Careful cleaning and inspection during a BO assessment is therefore very important(80).

There is interobserver variability amongst pathologists in diagnosing dysplasia, in particular low-grade dysplasia. Non expert GI pathologists tend to overcall dysplasia. All dysplasia should ideally be confirmed by expert GI pathologists however there is no clear well defined or validated criteria for what defines an expert(80).

1.1.9.2 Consequences of the limitations associated with endoscopic surveillance of Barrett's oesophagus

Due to the challenges associated with endoscopic surveillance a significant proportion of dysplasia is missed on initial endoscopic assessment. A systematic review and meta-analysis showed that the pooled proportion of missed HGD or OAC in all BO patients is 26.6%(82). Another meta-analysis showed that pooled proportion of post-endoscopy oesophageal cancer was 26% in all studies. The result was consistent at 3 and 5 year follow up(83).

A panel of experts have made recommendations to reduce the rate of missed dysplasia/ neoplasia including standardising reporting with the Prague criteria, spending adequate time assessing the

BO mucosa, using Seattle protocol biopsies and the use of high-definition white light and chromoendoscopy during endoscopic assessment(84)(80).

Efforts to improve endoscopic surveillance have focused on improving sampling techniques combined with AI enhanced assessment of pathology samples, using AI as an adjunct to endoscopic imaging , molecular biomarkers for the identification of dysplasia and risk stratifying patients and educational tools to improve non expert endoscopists recognition of dysplasia in BO(80).

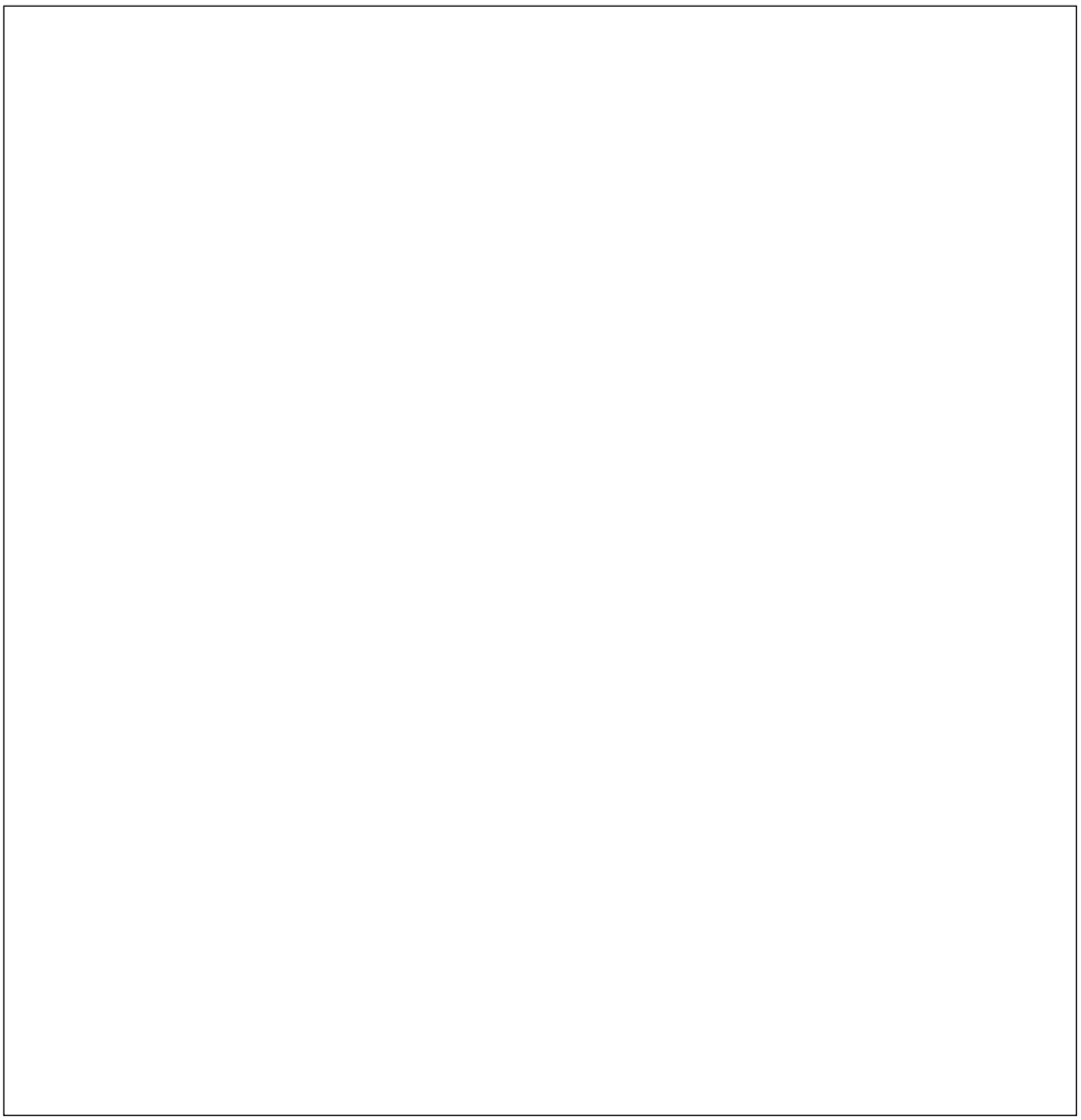


Figure 6: Surveillance intervals for non-dysplastic Barrett's. Image courtesy of Fitzgerald et al(7).

1.1.9.3 The BOSS study – does Barrett's surveillance improve cancer survival?

BOSS (Barrett's Oesophagus Surveillance Versus Endoscopy at Need Study) was a randomised controlled trial carried out at 109 centres in the UK. Patients were randomised to an 'at-need' endoscopy based on symptoms or a 2 yearly surveillance endoscopy. The primary outcome was overall survival(85).

3453 patients were recruited, and the median follow up time was 12.8 years for the primary outcome. There was no difference in overall survival between the two study arms. There was also no difference in cancer-specific survival. The authors concluded surveillance did not improve cancer specific and overall survival. They proposed that an as required endoscopy may be a safe alternative for low-risk Barrett's surveillance patients(85).

The study highlights several important areas to consider. There should potentially be a shift towards more focused, high quality and risk stratified Barrett's surveillance endoscopies. The cancers missed in the BOSS trial may be secondary to variables such as the skills of endoscopists and quality of equipment. One option is to introduce quality indicators like in colonoscopy or to limit higher risk endoscopies to expert centres. This is also potentially where Artificial intelligence systems like that discussed in chapters 3 and 4 of this thesis may play a role in improving both quality and dysplasia detection rates in endoscopy. It would increase confidence that those discharged from surveillance have had an optimal endoscopy as well improving detection rates on the higher risk patients that would continue endoscopic surveillance. Artificial intelligence can potentially play a role in endoscopic assessment and histological assessment where it can minimise interobserver variation and potentially also predict future risk of progression. A tissue systems pathology test called tissue cypher has been shown to be a strong predictor of incident progression in patients with BO(86).

Another option to consider would be offering capsule-sponge tests to patients not offered endoscopic surveillance. This can be done in the community therefore reducing the burden on secondary care(86).

The result of this study encourages Gastroenterologists to think about streamlining how we monitor BO surveillance patients. There were some limitations associated with this study which must be kept in mind when interpreting the results. Since the study there has been advances in endoscopic imaging technology which will likely have an impact on dysplasia detection rates

and therefore potentially impact mortality. At the start of the trial patients without intestinal metaplasia (25% of patients) were included reflecting UK guidance at the time. There was contamination between the two groups. Clinicians were not monitored for following standard of care Seattle protocol biopsies(85).

Overall, these are significant findings and should be considered in management strategies for BO in future.

1.1.10 Chemoprevention strategies for Barrett's oesophagus

There is a poor prognosis associated with oesophageal cancer. Therefore, there has been a lot of interest over the years in research looking at chemo preventative measures to avoid the development or progression of dysplasia.

1.1.10.1 Acid suppression

Proton pump inhibitors (PPI) are widely used for the treatment of GORD. Studies have assessed its use in the prevention of development of BO with variable results. Some studies have shown that PPI's have a protective effect in patients with BO. A systematic review and meta-analysis showed that the use of a PPI is associated with a 71% reduction of the risk of progression to HGD and OAC in BO(87). One population-based case-control study showed that use of acid suppression medications long term was associated with an increased risk of OAC, however it was felt that this was explained by the underlying condition for PPI use which was the risk factor associated with the development of OAC.

1.1.10.2 Aspirin and non-steroidal anti-inflammatories

A pooled analysis of six population-based studies showed that patients that used Non-steroidal anti-inflammatories (NSAID) and aspirin had a significant reduction in the risk of developing oesophageal adenocarcinoma. There was an increased protective effect with an increase in the frequency and duration of NSAID use(88)(89).

A randomised control trial involving 84 centres showed that a combination of high dose PPI and aspirin when taken in combination improved survival in patients with BO if given for at least nine years(90).

1.1.10.3 Statins

A metanalysis showed a 28% reduction in the risk of oesophageal cancer amongst patients on statins. In patients with BO there was a 41% reduction in the risk of oesophageal adenocarcinoma. The overall conclusion from this meta-analysis was that statins protect against oesophageal cancer and reduce the risk of oesophageal adenocarcinoma in BO(91).

A case control study showed that statins were associated with a reduced risk of developing BO. The greatest level of risk reduction was seen in patients with a long segment of BO and in obese patients(92).

1.1.11 Imaging modalities in Barrett's oesophagus assessment

Imaging modalities in endoscopy can help support the detection and targeted biopsies of any abnormal areas in BO in addition to the standard Seattle protocol biopsies. The use of additional imaging modalities is a supportive adjunct to the Seattle protocol biopsies and is not currently a replacement for this.

1.1.11.1 High-definition white light

High-definition white light endoscopy (HD-WLE) is considered the gold standard baseline for the assessment of BO and is supported by guidelines(7)(56). Studies have shown that HD-WLE is superior to standard WLE for the detection of dysplasia in BO(93).

1.1.11.2 Virtual chromoendoscopy

This technology is built into the endoscope and there are different system options. It has the advantages in that it does not add any cost as its built into the endoscope. It also does not take added time to activate as it involves the pressing of a single button. There are also no risks to patients from using it(94).

1.1.11.2.1 Narrow band imaging

There is the Narrow Band Imaging (NBI) system from Olympus. This applies a red-green-blue filter on to the Barrett's mucosa. NBI uses shorter wavelengths than WLE to be able to highlight more clearly the surface vascular and mucosal pattern. NBI uses a narrow spectrum which

matches the maximum absorption of haemoglobin. The structures in the mucosa with a higher haemoglobin such as surface capillaries and submucosal vessels will appear darker. The surrounding mucosa appears lighter. A cross over randomised controlled trial showed that with use of NBI there was a higher detection rate of BO dysplasia (30% versus 21%, P = 0.01) and fewer biopsies were required per patient(95).

1.1.11.2.2 iScan optical enhancement

The iscan optical enhancement (OE) system (Pentax, Hoya, Japan) uses pre- and post-processing techniques to improve the visibility of the microvasculature and to provide a surface enhancement of the superficial mucosal architecture (Figure 7).

OE uses a new optical filter to deliver specific wavelengths of light which correspond with the main absorption spectrum of human haemoglobin (415nm, 540nm and 570nm) at a high light intensity. This allows the microvasculature in the superficial layers of the mucosa to be highlighted.

A prospective study showed that iScan OE improved dysplasia detection in BO and the accuracy of histological prediction compared to HD-WLE. The accuracy of dysplasia detection was higher in trainees that used OE versus HD WLE (76% versus 63%), the outcome was the same in the six experts when using OE versus HD WLE (84% versus 77%)(96).

According to guidelines a BO expert should meet the following criteria(56):

- An annual case load of at least 10 new patients with HGD/OAC in BO treated endoscopically
- They should have received additional training in the field of endoscopic therapy in BO with at least 30 supervised cases of endoscopic resection and at least 30 cases of endoscopic ablation therapy to acquire the necessary knowledge and competencies in the technical skills, treatment algorithms and management of complications.

Figure 7: Endoscopic assessment of the oesophagus during a pull through assessment starting from the distal end of the oesophagus to the proximal end. Imaging of distal, mid and proximal oesophagus segments in WL and iScan OE. Image courtesy of Everson et al(96)**.**

1.1.11.2.3 Blue light imaging

Blue light imaging (BLI)(Fujifilm) uses a 4-light emitting diode multilight technology which allows brighter images to be produced. This non filter technology produces blue light in a narrow spectrum which are bright enough to allow the detection of subtle abnormalities and changes in the vasculature and mucosal pit pattern(97) (Figure 6).

A prospective international study showed that BLI has an additional value to WL for the detection of Barrett's neoplasia. Experts were able to detect and delineate neoplasia in BO significantly better on BLI versus WLE(98).

Figure 8: Overview images of Barrett's oesophagus in forward view and retroflexion in white light(A) and blue laser imaging (B). De Groof et al(98)**.**

1.1.11.3 Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) uses laser light delivered via the endoscope (Figure 9). The light reflects though a pinhole and then onto sensors. These sensors relay signals to a computer which then provides cross sectional microscopic images of the mucosa. This allows real time analysis of in vivo histology. There is an endoscope-based CLE and probe-based CLE. The probe-based CLE allows for imaging of a small area of the mucosa at a time. This may be more useful to assess a small area of the Barrett's mucosa being considered for an endoscopic resection. It is limited due to narrow fields of view(99).

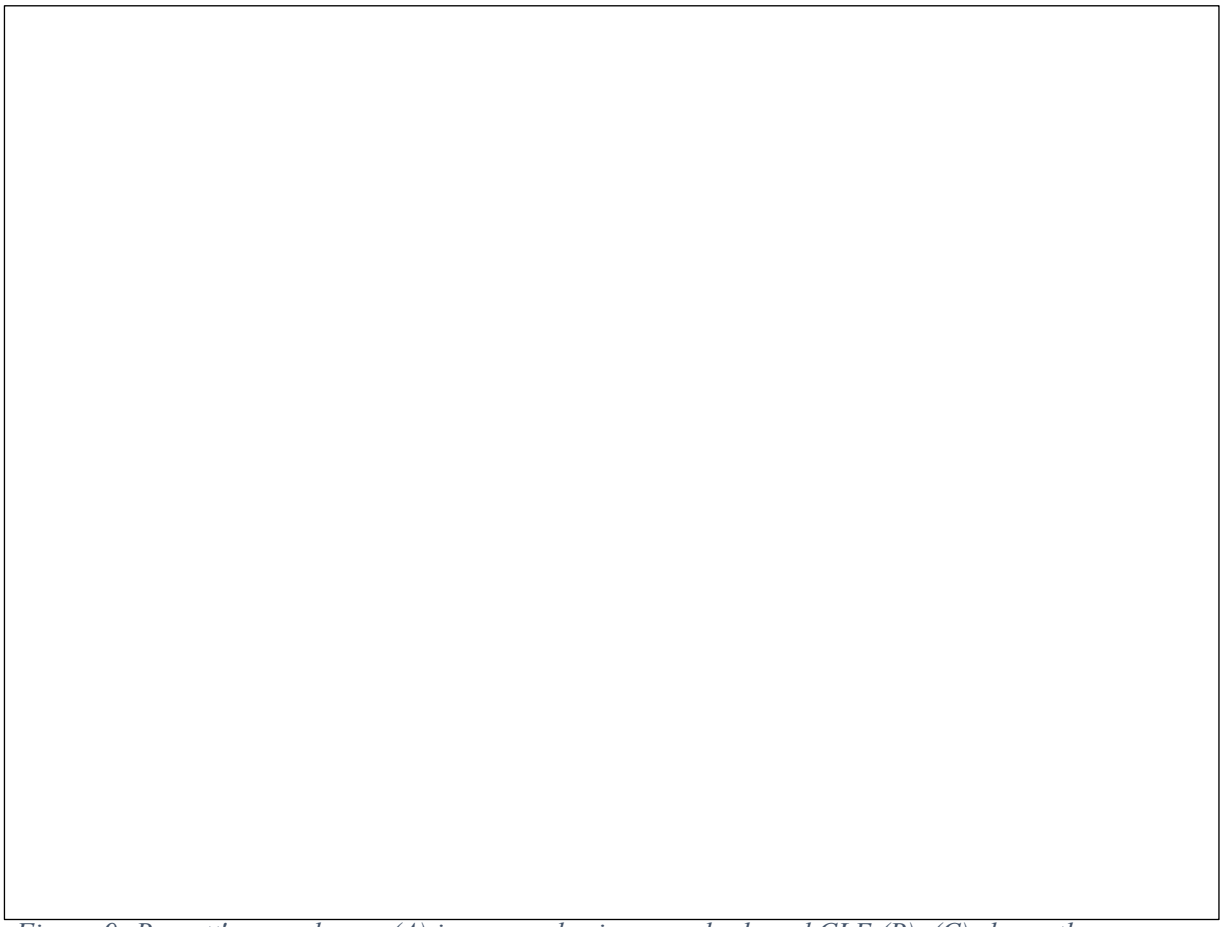


Figure 9: Barrett's oesophagus (A) is assessed using a probe-based CLE (B). (C) shows the histopathological view of an area of OAC. This is also assessed using probe CLE (D) showing irregular gland structures which are lined by atypical cylindrical cells (100).

1.1.11.4 Volumetric laser endomicroscopy

Volumetric laser endomicroscopy (VLE) (Ninepoint Medical, Bedford, MA, USA) uses infrared imaging to generate real time and high-resolution imaging of the Barrett's tissue microstructure. It can scan 6cm of the length of the oesophagus in 90 seconds. It provides both surface and also subsurface wide-field cross-sectional imaging with an axial resolution of 7 μm up to a depth of 3mm(99). (Figure 10 and 11)

The advantages of this imaging technology is that the area of abnormality can be laser marked, a large section of the oesophagus can be assessed in a short time period and there is limited interobserver variation between experts(99).

A retrospective study comparing VLE without laser marking, VLE with laser marking and Seattle protocol biopsies showed that there was a significantly higher yield of dysplasia detection when using VLE(101).

The disadvantage of VLE is that it presents large volumes of information which can be difficult to interpret in a short period of time. An artificial intelligence system called intelligent real-time image segmentation has been developed to overcome the issue of interpretation and assess the features of VLE which are associated with dysplasia(99).

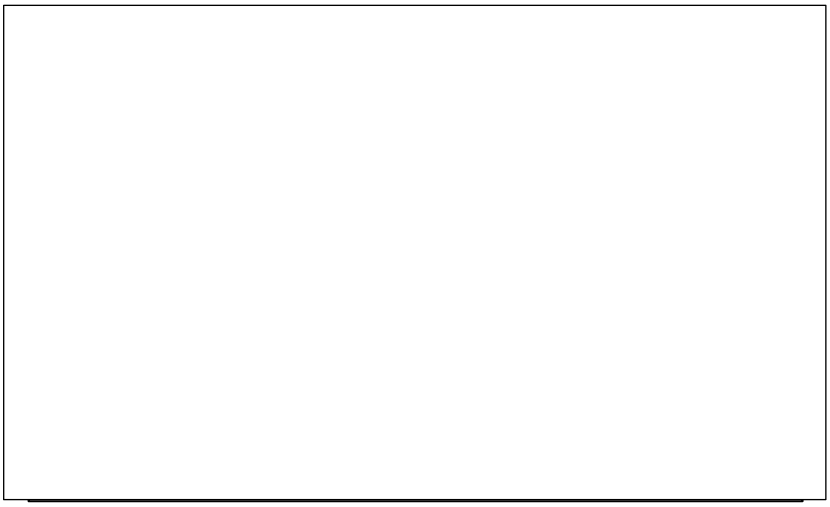


Figure 10:Nine-point medical VLE imaging system with a single optical probe

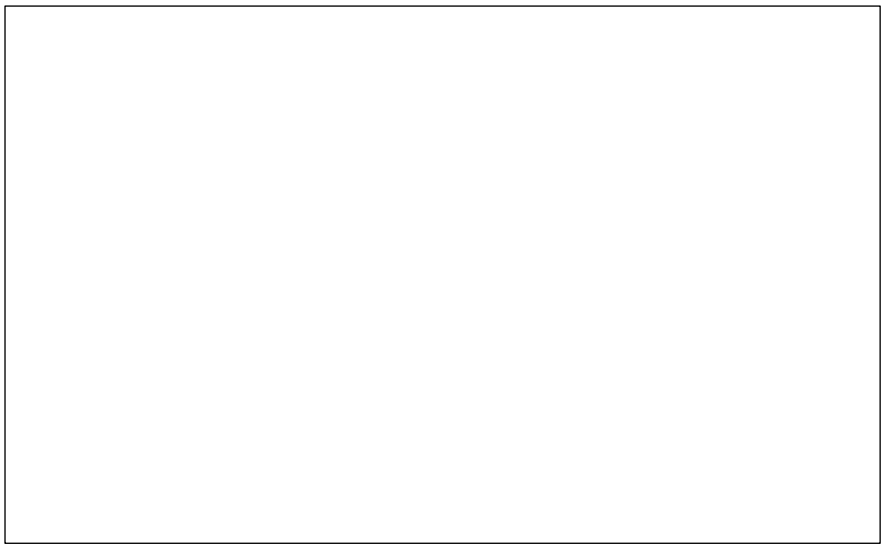


Figure 11: Examples of imaging on VLE. (A) Normal squamous epithelium, (B) Gastric cardia-gastric rugae and pit and crypt architecture (arrow), (C) NDBO-irregular surface, regular glands in epithelium (arrow), (D) dysplastic BO-thinning of the outer surface layer, atypical gland(102).

1.1.12 Endoscopic treatment for dysplasia in Barrett's oesophagus

Endoscopic therapy is offered to patients with intramucosal adenocarcinoma, High grade dysplasia and confirmed LGD i.e. confirmed and agreed upon by two separate pathologists and present in two separate endoscopies. The aim is for curative endoscopic therapy to minimise the risk of progression to an advanced malignancy.

1.1.12.1 Endoscopic mucosal resection and endoscopic submucosal dissection

This is the initial treatment option for nodular BO. This has the advantage of allowing accurate histological staging of a lesion and increases the chances of successful remission. In endoscopic mucosal resection (EMR) there are two techniques – band ligation and the cap assisted method. In the cap assisted method the lesion is suctioned into the cap therefore creating a pseudopolyp. This is then resected with an electrocautery snare. In the band ligation assisted method the lesion is suctioned, and the band ligation device is used to create the pseudopolyp. The lesion is then resected with an electrocautery snare(103). (Figure 12)

Endoscopic submucosal dissection (ESD) is a technique used to resect large BO lesions en bloc. An electrosurgical knife is used to dissect the submucosa below the lesion after injection of a lifting solution(104).

A prospective study of over 500 patients that had an ESD or EMR followed by ablation show a complete remission of dysplasia rate which was higher in the ESD cohort compared to the EMR group at the 2-year point. The complete remission of intestinal metaplasia rate was similair in both cohorts. There were no significant differences in the rates of endoscopic complications(105).

A randomised controlled trial comparing ESD and EMR for the treatment of BO with HGD and OAC showed that with ESD there was a higher en bloc resection rate compared to EMR (59% versus 12%). The remission rates at 3 months were similair. ESD procedure was more prolonged with a higher risk of complications versus an EMR(106).

The perforation rates following an endoscopic resection range between 0 and 5%. They are higher with ESD. Bleeding commonly occurs but can be controlled endoscopically with

coagulation forceps. The most common complication are oesophageal strictures. This risk increases with an increase in the size of the mucosal resection area(104).

1.1.12.2 Radiofrequency ablation

Radiofrequency ablation (RFA) is used to treat any residual BO following an index endoscopic resection of a lesion. It minimises the risk of progression and recurrence. It is also used for the treatment of flat dysplastic BO at index endoscopy if there is no lesions following endoscopic assessment (Figure 12).

RFA uses a bipolar electrode which is in direct contact with the BO mucosa. This generates heat and induces coagulative necrosis of the mucosa. There is a large volume of evidence which supports its efficacy and safety for the treatment of BO.

The United Kingdom RFA registry collected data on 335 patients with BO and neoplasia from 19 centres. It looked at the outcomes in these patients' following treatment with RFA. HGD was cleared from 86% of patients and all dysplasia from 81% of patients at the 12-month follow up time point. Shorter segments of BO responded better to RFA(107).

1.1.12.3 Argon plasma coagulation

This technique uses a through the scope catheter to ablate the Barrett's mucosa using argon gas. There is a high voltage current generated from the tip of the catheter which ionises the argon gas. The resulting plasma creates thermal energy which is used to coagulate the Barrett's mucosa(104). A randomised control trial showed that Argon plasma coagulation (APC) has a similair efficacy to RFA, and that APC was more favourable in terms of cost(108).

APC can be applied following submucosal lift using saline. This is called hybrid APC and has the advantage of minimising stricture formation. A prospective study of 146 patients showed that after 2 years 66% of patients had no recurrence of BO. There was a 4% rate of stricture formation(109).

1.1.12.4 C2 Cryoballoon ablation system

The C2 Cryoballoon ablation system consists of through the scope balloon catheters which are self-inflating and self-sizing. It is attached to a controller and this functions to control the level of flow of nitrous oxide through the balloon which then freezes the Barrett's mucosa. No thermal energy is required.

A systematic review and metanalysis of 7 studies showed that cryoablation was safe and effective for the treatment of BO neoplasia(110). A single centre study assessed the durability of Cryoballoon ablation treatment for BO with neoplasia. Patients had LGD, HGD or intramucosal adenocarcinoma at baseline/index endoscopy. Any visible lesions were removed by EMR prior to any ablation treatment. Using Cryoballoon ablation there was a complete eradication of dysplasia of 94% at one year, and complete eradication of intestinal metaplasia of 75% at one year. There was a cumulative rate of recurrence of 1.9% for dysplasia and 14.6% for intestinal metaplasia. No patients progressed to neoplasia on treatment. Post procedure bleeding occurred in one patient that was on clopidogrel. 5 out of 59 patients developed strictures post ablation that required balloon dilatation (111).

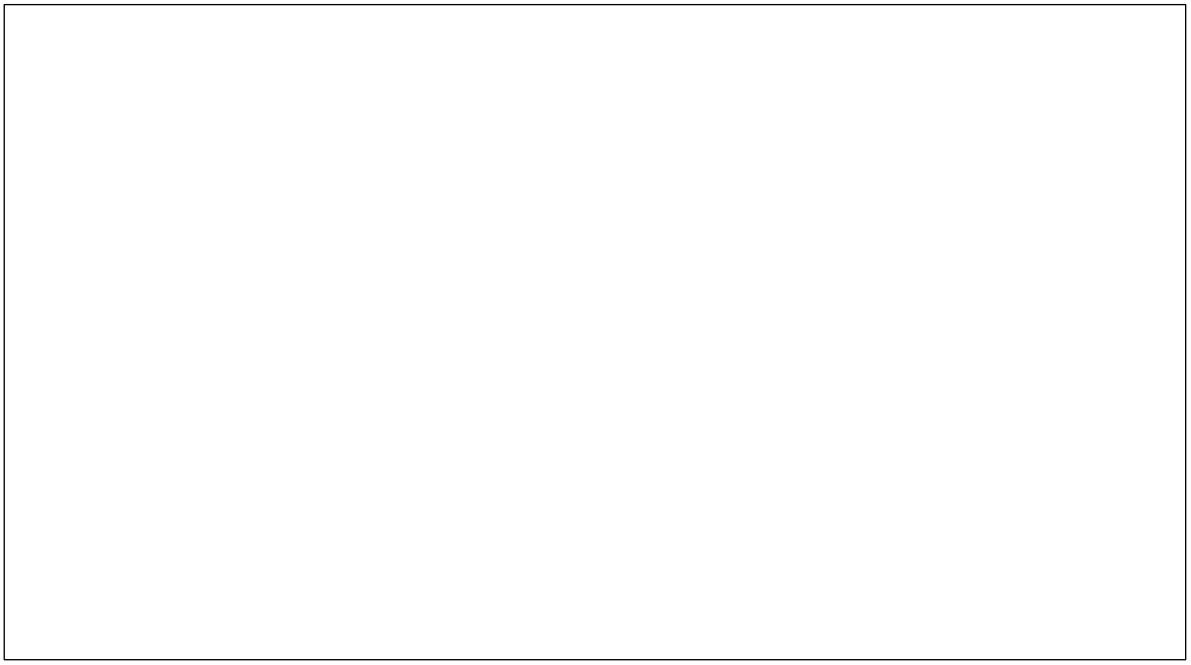


Figure 12: Endoscopic mucosal resection and radiofrequency ablation treatment of Barrett's oesophagus. Images courtesy of Apostolis et al

1.1.13 The current problems with neoplasia detection and surveillance of Barrett's oesophagus

There are a few problems currently faced in early lesion detection and surveillance strategies for Barrett's oesophagus. The suite of studies in chapters 2, 3 and 4 in this thesis will address some of these issues and pave the way for randomised control trials that will potentially improve early detection strategies:

1- There is a poor adherence to Seattle protocols for biopsy of BO. A study of more than 2000 BO surveillance patients showed that there was only a 51.2% adherence to the Seattle protocol which was poorer in longer segments(112). In a further study of 150 patients there was an only 30% adherence to the protocol in patients with a segment longer than 10cm(113). These patients are at higher risk of developing OAC. A recent population-based analysis assessed adherence to seattle protocol biopsies in 572 endoscopists. Adherance to Seattle protocol biopsies varied by endoscopists and also by site. There was an overall dysplasia detection rate in BO of 3.1% and again this was variable based on endoscopists and site(114). There is a need for adjunct tools to minimise miss rates of lesions and support a more targeted biopsy approach which would support better adherence(115). This would potentially help better standardise BO assessment and minimise the variations in dysplasia detection rates with higher detection in expert centres, and under detection in non-expert units.

2- Even when the Seattle protocol biopsies are adhered to approximately 4-6% of the Barrett's segment is sampled. There can be subtle mucosal changes in the areas not sampled which can be missed by non-experts(116)(115). A recent retrospective analysis evaluated 614 patients with BO on index endoscopy. 4.1% had definite dysplasia, and 14% had indefinite for dysplasia in BO on repeat endoscopies within 18 months of the index endoscopy with NDBO(87).

3- There are interobserver variations between pathologists in the detection of LGD. There is difficulty in differentiating between true LGD and inflammatory changes in the oesophagus(115)(36)(35). The study in chapter 2 of this thesis looks into this issue.

There is a need for adjuncts like artificial intelligence to help support endoscopists with early dysplasia/cancer detection strategies and minimise dysplasia miss rates.

1.2 Artificial intelligence for the detection of dysplasia and cancer in Barrett's oesophagus

Increased efforts are required to improve the early detection of oesophageal cancer. As discussed in this introduction chapter thus far a few endoscopic and non-endoscopic potential screening options have been developed to improve early detection of oesophageal cancer so that curative endoscopic therapy can be offered. Computer aided diagnosis will play an important role in the coming years for the early detection and characterisation of lesions in the GI tract.

Artificial intelligence (AI) has become increasingly popular in the last decade. This is likely due to a combination of the increase of the computational power of modern computers and due to the introduction of deep learning. AI has advantages over human endoscopists due to the lack of varied interobserver disagreement, there will be no human fatigue and there will be no requirement of learning curves for it to be trained. AI will potentially help support neoplasia detection and characterisation, and also potentially help support improvement in endoscopy quality through real time feedback to the endoscopists regarding procedure metrics (117).

1.2.1 Definitions

This section will describe the definitions and descriptions of terminology to allow a better understanding of the studies in chapter 3 and 4 in the thesis.

Artificial intelligence

The term Artificial intelligence (AI) refers to a much larger field which includes machine learning, natural language processing and reasoning(118).

Machine learning

Machine learning is a methodology which creates mathematical models in order to capture structure inside a data set. This can then make a prediction about any new data which has not been seen or used to train these models. This can be divided into supervised and non-supervised learning subtypes. Supervised learning is when data is provided with specific labels for example in the case of Barrett's 'dysplastic' or 'non-dysplastic'. When no labels are provided for the training data this is called unsupervised learning(119).

Deep learning

Deep learning is a subtype of machine learning. The model is referred to as a neural network and is composed of several layers. This allows for the automatic learning of features in an image or video. This is useful in developing an AI model using endoscopic images where there is a lack of a distinct structure and it's not easy to subdivide into specific types of features.

Convolutional neural network

A convolutional neural network (CNN) is a subtype of deep learning. It can learn specific features from endoscopic images or videos inputted into the network. For example, in Barrett's assessment this would be the pit pattern, size of a lesion and vascular pattern. This complex array of information is then processed through the many different layers of the CNN and a prediction output is generated for example dysplastic/non-dysplastic Barrett's oesophagus (Figure 13).

Data Augmentation

This is a process of artificially enhancing the size of the data set by making slight adjustments to the data in the training set. The adjustments do not impact on the labels such that they do not change. The adjustments made can be random affine transformations (rotation, translation and scale) and random colour transformations (brightness, contrast, saturation and hue). The process of data augmentation leads to a more robust model.

Pre-training

This involves training the algorithm using a different set of data from the target data. A rough model can be initially created using a large data set which can then be fine-tuned using the target training data set. For example, training a model with random images of the GI tract and then fine-tuning with a smaller target data set for example Barrett's oesophagus images.

Hyperparameters

Machine learning models are regulated by hyperparameters. These govern the architecture of the model and the way that it is trained. They can alter the performance and behaviour of a model. There are two types of hyperparameters which are relevant to the development of neural networks. They are training hyperparameters which determine the process of training such as the learning rate. The second are model hyperparameters which contribute to the definition of the architecture of the model such as for example the number of neural layers. (118).

Hyperparameter optimisation

This is the process of finding the right hyperparameter for a model based on performances on the validation set. This performance can be assessed through a grid search, where there are a number of options that are defined for each hyperparameter and all combinations are evaluated in a systematic way. Alternatively this can be done with a random search where values are randomly sampled from a predefined range(118).

Backpropagation

This is a method for training a neural network to minimise error. The network makes a prediction for a sample, any error is then propagated back through the network to allow for updating of any network weights and therefore minimise any errors. This is repeated multiple times for all data points until the error does not significantly decrease any further (Converge).(118)

Mini batches

This is a subset of the training set which is computed by the model following which there is an update to weights and gradients. The mini batches are sampled randomly and not replaced. Once there are no further data points that are left, then it is considered that one epoch has been completed.

Epoch

During the process of backpropagation all the data points would pass through the neural network either individually or as part of mini batches to both minimise any error and to update the model. An epoch is the period during which all the data points have passed through the network on one occasion(118). Essentially when the whole training set is seen by the model, this is the equivalent of one epoch.

Learning rate

Whilst the neural network is being trained the model would adjust its weights until the prediction errors on the data is kept to a minimum.(118)

Residual Networks for classification

Residual networks (ResNet) are convolutional neural networks which help in the training of deep and very efficient networks for classification. Normally with an increasing depth to the network the accuracy of prediction declines due to saturation. Therefore, in residual networks there are

skip connections which overcome this problem of decline in accuracy. This allows gradients to flow through more effectively and allow the deeper networks to be trained. ResNet can come in several versions depending on the number of layers in the network.

The ResNet consists of residual blocks. Each block consists of a mini batch of layers from the CNN. There are skip connections which skip over some neural layers. The neural layer blocks can focus on learning what is needed to add to the input in order to get the desired output. This process ensures that the layers higher up are as effective as the layers further below. Blocks can be stacked to build deep learning networks without losing the learning ability(120).

ResNets are easy to optimise and can also easily gain the required accuracy from increasing the depth of the networks.

Classification

This is a type of supervised learning. The input normally consists of numerical data such as for example images. The aim is to match the input with a class of predefined categories for example dysplasia versus no dysplasia, or class of polyp (hyperplastic versus adenoma).(118)

Segmentation

This is a type of supervised learning. The input is an image, and the aim is to segment a part of that into a specific category in the output. The output is a numerical mask. For example, in the case of Barrett's oesophagus delineation of a lesion on an image.(118)

Spatio-Temporal filtering

Endoscopists assess a lesion in the GI tract over a few consecutive frames to allow for a prediction to be made. In a similair way an exponential weighted average of consecutive frames can be used to make a diagnosis.

Computer aided detection (CADe)

These are machine learning algorithms developed to allow for the detection of pathology for example dysplasia in Barrett's oesophagus or polyps in the colon.

Computer aided diagnosis (CADx)

These are machine learning algorithms developed to allow for the prediction of the diagnosis for example the classification of a polyp in the colon or the histology on the Barrett's oesophagus image.

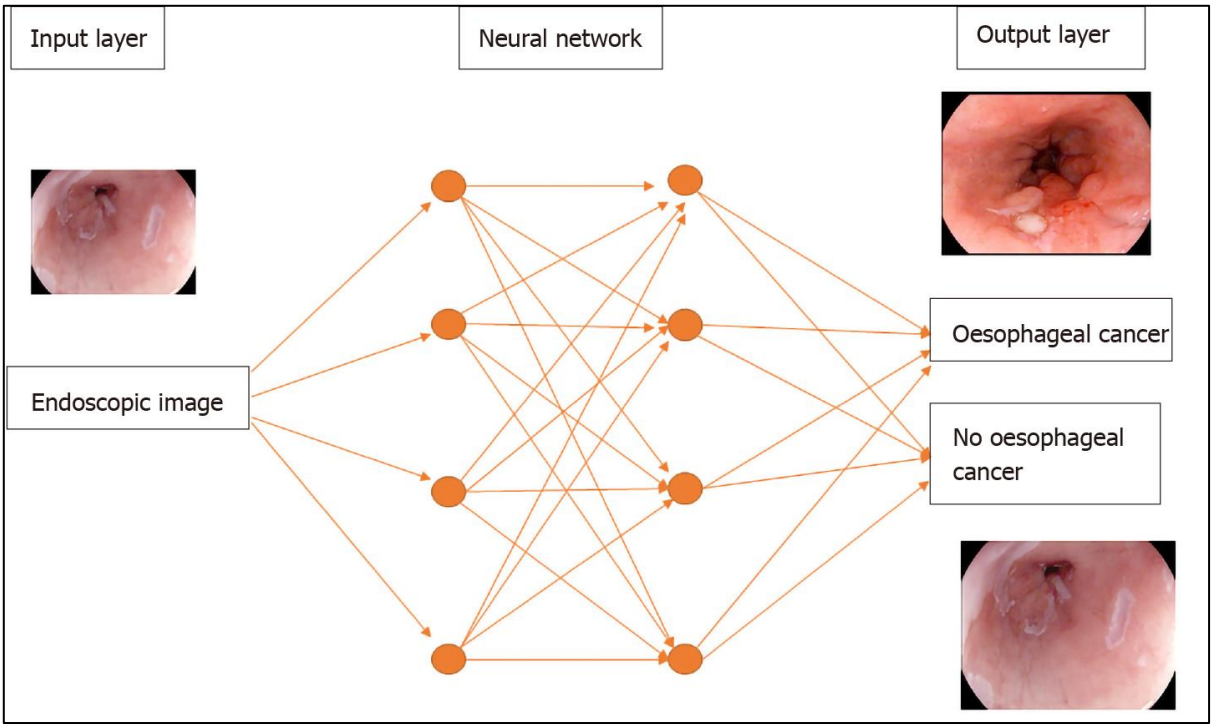


Figure 13:An example of a deep learning model for the prediction of early cancer in Barrett's oesophagus. Features of an endoscopic image are processed through the many different layers of the network so that features are learned. The model is then able to make an independent prediction on unseen images on the presence/absence of oesophageal cancer. Images courtesy of Hussein et al(119)**.**

Overfitting of the training data set

There are different types of available machine learning models that can be used to describe the relationship between the input, for example an image of the oesophagus, and the output, for example the delineation of an area of cancer in the oesophagus. All machine learning models use data to be built. This is called training. During the process of training, with the support of mathematical optimisation models, the machine learning models will continue to gradually improve by capturing the relationship in the input and output in the training data set. Once the process of training has been completed the models should be able to work on making predictions on unseen data. If model only works on the training data, but not on the new data then this is defined as overfitting. The models are fitted to the training data but are not able to generalise to make predictions on any new data. This is a bigger issue for data sets which are small and also for models which are complex (118).

1.2.2 Training, validation and test sets

To develop a machine learning model data is normally split into independent training, validation and testing data sets. The training data set is used to train and build the model to be able to predict specific features on an endoscopic image or video for example presence or absence of dysplasia. The validation data set is used to test the ability of the trained model to make a prediction on data that is not seen. It also ensures that there is no overfitting of data when training the model. Hyperparameters can be tuned to optimise the performance of the models depending on the predictions made on the validation data set for example the number of layers in the neural network. The testing data set is used to evaluate the performance of the final model on an unseen data set. Overfitting means that the model is able to perform well on the training data set but not on data that is unseen i.e. the testing data set (Figure 14)(118).

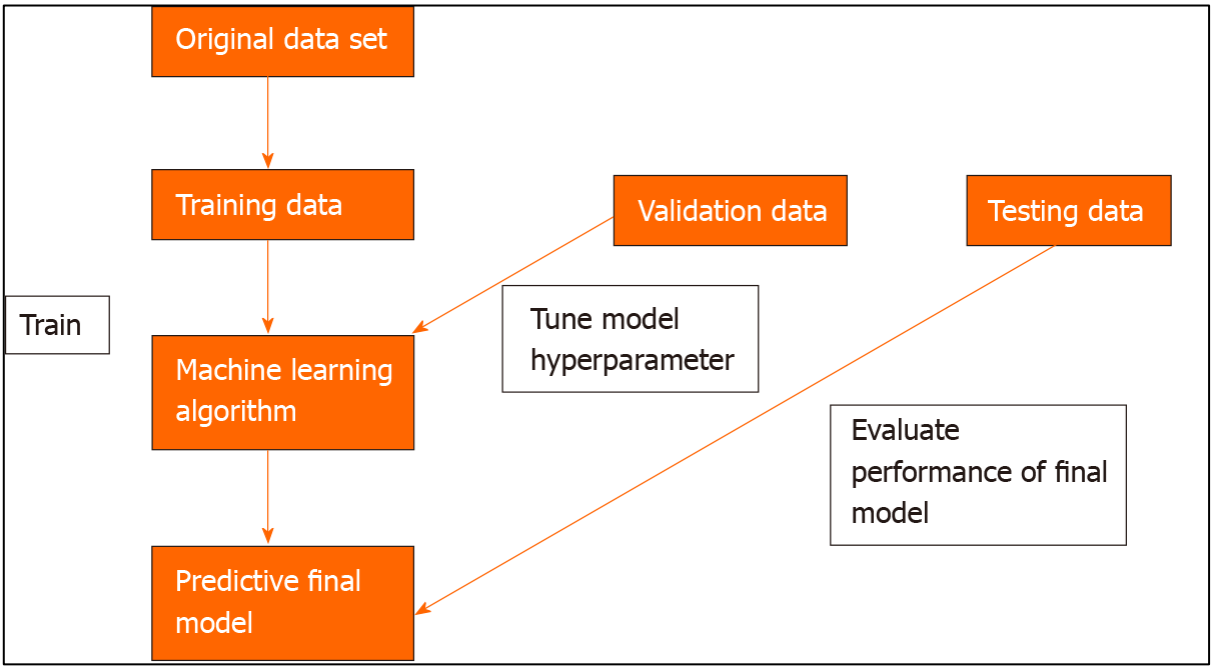


Figure 14: A machine learning model is created using three independent data sets - training, validation and testing data set. Image courtesy of Hussein et al(119).

1.2.3 Cross-validation

There is often a limit in the amount of available endoscopic data to train a machine learning model. Therefore, other methodologies are used to make use of the available data. In cross-

validation data is split into several equal parts for example four. Three parts are used for training and the remaining data is used for validation. This process is repeated four times with a different validation set each time (Figure 9).

The data in the different sections need to be split on a patient basis i.e. data from one patient can appear in either the training or validation set(118).

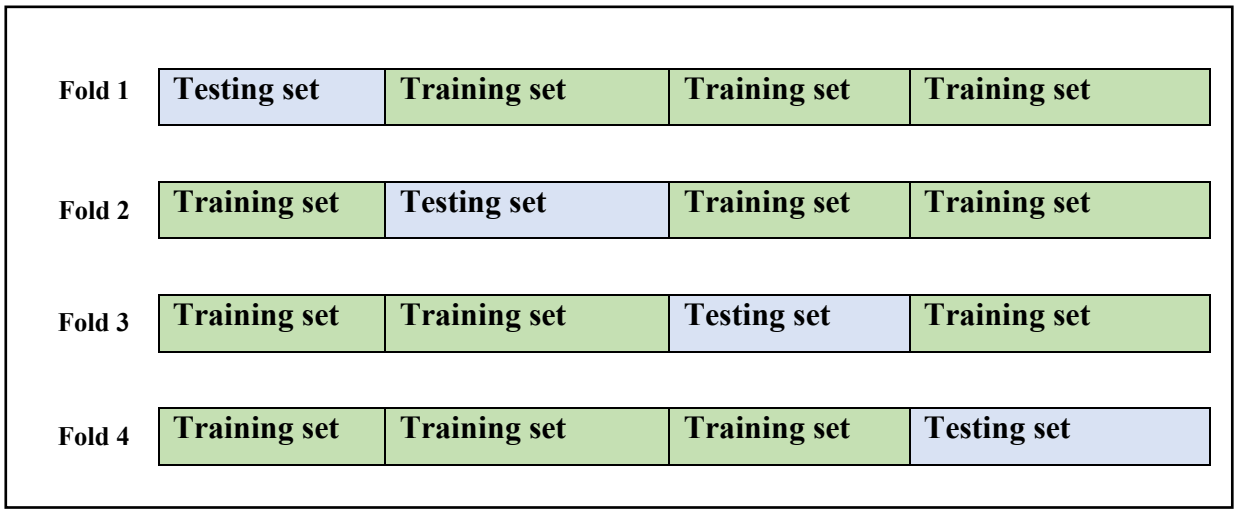


Figure 15: A 4-fold cross validation model. Data is split into four equal parts. Three parts are used for training and one part for validation. A different part of the data set is used for validation each time.

1.2.4 Developing a gold standard

The gold standard or the ground truth is the labels that are used to train the algorithm. The labelling of the data needs to be reliable as this is how the model will be trained to make predictions on an endoscopic image or video.

The gold standard provided depends on the predictions required of the model. For example, for computer aided characterisation the gold standard would be the histology. For prediction of location of the area of interest the gold standard would be expert annotation labels on images. There is normally interobserver variability between endoscopists for pixel precise annotations which is why a larger number of annotations from different experts are preferrable(118).

1.2.5 Studies on neural networks for the detection of dysplasia and cancer in Barrett's oesophagus

The current standard of care for BO surveillance is to take Seattle protocol biopsies every 2cm within a segment of BO. This methodology can be associated with sampling error and furthermore Seattle protocol biopsies would only cover a small area of Barrett's(116). Dysplasia in a Barrett's segment can be focal and can hypothetically be missed with Seattle protocol biopsies. Studies have also shown that compliance with Seattle protocol is poor(112). Artificial intelligence provides a potential way to support endoscopists by optimising the detection of dysplasia in BO with a minimal number of biopsies.

The studies that have looked at the development of neural networks for the detection and characterisation of BO can be divided into CADe and CADx studies. The next two sections summarise the studies that were done at the time of publishing the AI studies on CADe and CADx in chapters 3 and 4 of the thesis respectively.

1.2.5.1 Computer aided detection studies in Barrett's oesophagus

The detection of early cancer in BO can be a challenging task for non-expert endoscopists. Training an AI system to the same level of expertise as an expert BO endoscopist could be a potential game changer in minimising early cancer miss rates.

The first study where an algorithm for the detection of early cancer in BO was developed based on 100 images from 44 patients. The training was done using texture and colour filters. Neoplastic lesions were detected on a per image level with a specificity and sensitivity of 0.83. At a patient level the algorithm achieved a sensitivity and specificity of 0.86 and 0.87 respectively(121).

In 2019 the ARGOS consortium developed a CADe system based on images developed over a series of two publications. The CADe was able to diagnose dysplastic BO with a sensitivity of 90% and specificity of 88%. It performed better than non-expert endoscopists. The studies were performed using Olympus and Fujinon endoscopes(122)(123).

The same group tested the performance of the CADe in the endoscopy unit during a live procedure. This included 10 patients with BO dysplasia and 10 patients with non-dysplastic BO. Three images were assessed every 2cm of BO by the CAD system providing real time feedback to the endoscopist. Three images were analysed by the CADe system every 2cm of BO. On a per

level analysis the CADe system achieved a sensitivity and specificity of 91% and 89% respectively. 9 out of 10 patients were correctly diagnosed with dysplasia(124).

The same group developed a CAD system using five independent endoscopy data sets. This was pre trained using 494,364 labelled endoscopic images of the GI tract. The performance of the CAD system was compared against 53 general endoscopists to allow benchmarking of the performance of the CAD system. The CAD system classified images with a 89% accuracy, 90% sensitivity and 88% specificity for dysplasia. In a separate test set the performance was better than endoscopists (88% vs 73% accuracy, 93% vs 72% sensitivity, and 83% vs 74% specificity)(123). The dataset was from Olympus and Fujifilm endoscopes.

Hashimoto et al developed an image-based CADe system that works on an Olympus data set. A CNN was pre-trained on ImageNet. It detected dysplasia with a sensitivity of 96.4% and specificity of 94.2%. The object detection algorithm was able to localise dysplasia with boxes with a high accuracy and real-time implementation speeds(125).

Ebigbo et al demonstrated real time application of a deep learning AI system for the diagnosis of early cancer in BO. The positive histology in this study were all adenocarcinomas. The system was trained using 129 endoscopic images. This was tested on 62 images from 14 patients. Early cancer was detected by the AI system with a sensitivity of 83.7% and specificity of 100%(126).

At the time of writing this thesis there was no studies that demonstrated the development of an AI system specifically for the detection of BO dysplasia using the Pentax endoscopic system. The studies discussed in this section were the only studies published in this area in peer reviewed journals at the time of publishing the CADe work discussed in chapter 3 of this thesis(127).

1.2.5.2 Computer aided diagnosis studies in Barrett's oesophagus

The CADx studies for the characterisation of BO dysplasia are much more limited. This would potentially form an important part of a two-step AI system. Step one would be the CADe working to detect the area of abnormality during a pull through assessment of the oesophagus. Step 2 would be the CADx which would confirm the diagnosis and help potentially delineate the margins for an endoscopic resection.

Ebigbo et al trained a CADx system using a publicly available data set and an internal data set. This consisted of white light and NBI data. This demonstrated high accuracy. The study size was limited but this study demonstrated the feasibility of a CADx system for Barrett's oesophagus(128)(117).

Struyvenberg at al developed a CADx system which characterises dysplasia on NBI magnification images(129). Four-fold cross validation was used to assess the performance. The system demonstrated a sensitivity and specificity of 88% and 78% respectively for the detection of BO dysplasia on NBI zoom images. A video-based CAD system tested on 30,021 video frames demonstrated a sensitivity and specificity of 85% and 83% respectively for the detection of BO neoplasia. The average assessment speed was 38 frames per second(129).

The CADx systems would provide a potential way of supporting the CADe systems for the detection of early cancer in BO.

At the time of writing this thesis there was no publications on the development of a CADx system which was based on the pentax iscan imaging. At the time of publishing the work detailed in chapter 4 of this thesis the studies discussed in this section were the only studies published in peer reviewed journals on CADx systems for characterising dysplasia in BO.

1.3 Gastrointestinal bleeding secondary to oesophageal cancer and post endoscopic therapy

One of the most common and challenging medical emergencies are GI bleeds. Despite advances in endoscopic therapy in the last two decades there is still a significant rate of mortality secondary to this. Endoscopy is the first line and gold standard treatment option.

Most upper GI bleeds are non-variceal in aetiology. The majority are secondary to peptic ulcer disease. An early endoscopy within 24 hours of presentation is recommended for most patients such that a quick diagnosis is reached, and haemostasis achieved(130).

1.3.1 The current problem

Upper GI bleeding is associated with significant mortality and morbidity(131). Advances in endoscopic technology will mean that more early GI cancers are identified, and curative therapeutic endoscopic options can be offered to patients. With more advanced therapy there are higher associated risks of GI bleeding and there needs to be an understanding of how this can be managed. Bleeding occurs in approximately 1-6% of cases after endoscopic mucosal dissection and 1-2% of cases following an endoscopic mucosal resection(132). Despite the risks of bleeding these procedures help offer an important organ preserving intervention.

The topic of post procedure bleeding is explored in chapter 5 of the thesis which looks at the outcomes of the use of a haemostatic powder called TC-325 (Haemospray, Cook Medical, USA) for the management of GI bleeding secondary to endoscopic therapy in the oesophagus.

On the other hand, despite advances in technology there is still a significant miss rate of early cancers of the oesophagus. These can then potentially progress into incurable and malignant tumours. These tumours can then bleed which is can often be difficult manage. GI bleeding secondary to tumours accounts for 5% of all UGI bleeds(133). Standard first line endoscopic treatment modalities have poor haemostasis rates as low as 40% and re-bleeding rates of up to 30%(134). Treatment methods can be limited by the need of direct contact with an already fragile tumour surface which can potentially exacerbate any bleeding.

The topic of management of oesophageal malignancy related bleeding is explored in chapter 6 of this thesis which looks at the outcomes of TC-325 for the management of GI bleeding

secondary to oesophageal malignancy as part of a multicentre international registry. This shows the added importance of advances like AI (chapters 3 and 4) to help minimise cancer miss rate and prevent such potential complications with advanced oesophageal malignancy which would impact on overall mortality and morbidity rates.

1.3.2 Risk stratification tools

It is important to risk stratify patients early following index presentation with a GI bleed. This is particularly important to help stratify how urgently a patient needs an endoscopy. There are three main scoring systems – Glasgow-Blatchford score, Rockall score and the AIM65 score.

1.3.2.1 Glasgow-Blatchford score

This scoring system uses a combination of blood parameters (Haemoglobin, urea) and clinical parameters (Systolic blood pressure, melaena, heart rate, presence of liver disease and heart failure, syncope on presentation) (Table 2). This helps determine if patients can be managed as an outpatient. Patients with a score of 0 or 1 can be safely discharged from hospital and outpatient endoscopy can be arranged(130)(135).

1.3.2.2 Rockall score

This predicts risk of mortality and re-bleeding by combining clinical and endoscopic parameters. Table 3 summarises the Rockall scoring system depending on different parameters. The maximum score before endoscopic diagnosis is 7, and after endoscopic diagnosis is 11. If the full Rockall score (post endoscopy) is less than 3 there is a low risk of re-bleeding or mortality, and patients can be discharged early. If the Rockall score is more than 5 the mortality risk is more than 11%, and the re-bleeding risk more than 24%. A Rockall score of more than 8 is associated with a high mortality(136). Age, shock and comorbidities form part of the initial (pre-endoscopic) score criteria. Diagnosis and major stigmata of major haemorrhage formulate part of the additional criteria that complete the full Rockall score (Table 3)

Table 2: Glasgow-Blatchford scoring system (130)

	Score
Blood urea (mmol/L)	
6.5 – 7.9	2
9 – 9.9	3
10- 25	4
>25	6
Haemoglobin for men (g/dL)	
12-12.9	1
10-11.9	3
<10	6
Haemoglobin for women (g/dL)	
10-11.9	1
<10	6
Systolic blood pressure (mm Hg)	
100-109	1
90-99	2
<90	3
Other markers	
Pulse ≥ 100/min	1
Malaena	1
Syncope	2
Liver disease	2
Heart failuire	2

Table 3: Rockall scoring system (130)

	0	1	2	3
Initial score				
Age	<60	60-79	>80	
Shock	No shock	HR > 100	HR >100, SBP< 100	
Comorbidity	No major co-morbidity		Cardiac failure Ischaemic heart disease Major comorbidity	Liver failure Renal failure Disseminated malignancy
Additional criteria for full Rockall score				
Diagnosis	Mallory-weiss No stigmata of recent haemorrhage No lesion	All other diagnosis	Upper gastrointestinal malignancy	
Stigmata of recent haemorrhage	None/dark spot		Fresh blood Visible/spurting vessel Adherant clot	

HR – heart rate, SBP – Systolic blood pressure

1.3.2.3 AIM65

This predicts length of stay, in hospital mortality and the associated costs of GI bleeding. It is superior compared to the Rockall and Glasgow-Blatchford score in predicting in-hospital mortality, but more inferior in prediction of re-bleeding(137)(138).

1.3.3 First line endoscopic treatment options for non-variceal Gastrointestinal bleeding

There are several treatment options available for endoscopic management of GI bleeds depending on the underlying aetiology.

1.3.3.1 Thermocoagulation

Thermal energy is used in direct contact with the area of bleeding. The heater probe has a Teflon-coated hollow aluminium cylinder and an inner heating coil. An electrical current is used to be able to generate heat. A gold probe has a gold distal tip which has good conductivity. It can also be used for injection and irrigation as well has heat delivery.

Argon plasma coagulation is a non-contact form of treatment where ionised gas is used to be able to conduct electricity for coagulation of the bleeding site.

1.3.3.2 Clips

Through-the-scope endoscopic clips work by obstructing the flow of blood through the vessel. The clip design has improved over the years to aid usability in terms of rotation, reopening and size. This is particularly important when there is a specific target. It has the benefit of lack of thermal injury to the tissue. It has the disadvantages of not being effective on fibrotic ulcers or in areas where endoscopic access is difficult. Met-analysis studies have shown that clips were superior to adrenaline injection monotherapy for achieving haemostasis, and comparable to thermal coagulation(139)(140)(141).

Over the scope clips are larger than standard through the scope clips and can be used in large fibrotic ulcers. A multicentre study in patients with recurrent GI bleeding showed that patients treated with the over the scope clip had significantly less re-bleeding compared with the standard of care(142)(143).

1.3.3.3 Epinephrine injection

This involves the injection of dilute epinephrine to reduce the flow of blood and therefore create a temporary tamponade in the local area with the vasoconstriction of blood vessels. A randomised study in a single centre showed that injection of 30ml of diluted epinephrine (1:10000) in a spurting or oozing ulcer bleed would be effective in the prevention of re-bleeding with low associated complication rate(144).

1.3.3.4 Monotherapy versus combination therapy treatment

Dual endoscopic therapy is considered superior to monotherapy with epinephrine injection for the endoscopic management of patients that have a high-risk peptic ulcer bleed. Dual therapy reduces the risk of requiring emergency surgery, mortality and re-bleeding risk(145)(146)(130).

1.3.4 Haemostatic powders for the management of gastrointestinal bleeding

To date there are five haemostatic powders for the management of GI bleeding. These are TC-325 (Haemospray, Cook Medical, Winston-Salem, NC, USA), EndoClot (EndoClot Plus, Santa Clara, CA, USA), Ankaferd Blood stopper (ABS, Ankaferd Health Products, Istanbul, Turkey), Nexpowder (Republic of Korea) and CEGP-003 (CGBio, Seong-Nam, Republic of Korea).

All these haemostatic powders use a catheter for the endoscopic delivery of the powder to the site of bleeding. They generally have the advantages of being easy to be trained on to use, can be applied to sites with tricky endoscopic access, can be applied to areas with widespread bleeding and does not require direct contact with a bleeding surface(147).

Chapters 5 and 6 of this thesis will focus on the use of TC-325 for the management of GI bleeding following oesophageal endoscopic therapy and secondary to advanced oesophageal malignancy.

1.3.4.1 TC-325

TC-325 consists of mineral granules. In contact with bleeding the granules absorb water from the blood. It then expands and adheres to the site of bleeding allowing haemostasis to be achieved (Figure 16). It was first assessed in a pilot study for the management of peptic ulcer bleeds. There was an immediate haemostasis rate of 95% and the safety profile was considered excellent with no treatment or procedure related adverse events(148).

The powder is delivered through a catheter. If this gets into contact with fluid or moisture, then this may block the catheter. Therefore, any contact needs to be avoided(149). The catheter is inserted through the channel of the endoscope and is normally held 1-2cm away from the bleeding source. The device consists of a C02 powder cartridge. This is activated by turning a red knob. There is a red valve at the top of the device which needs to be turned to open the position. There is a red trigger button which can be used to activate application of TC-325. This is short 1-2 second pulses(150)(Figure 17).

An advantage of TC-325 over standard first line endoscopic treatments is no direct contact is needed with the bleeding surface and it is easy to use and therefore does not require high endoscopic expertise. It can also be applied over a large surface area without the need for direct contact with the mucosal surface.

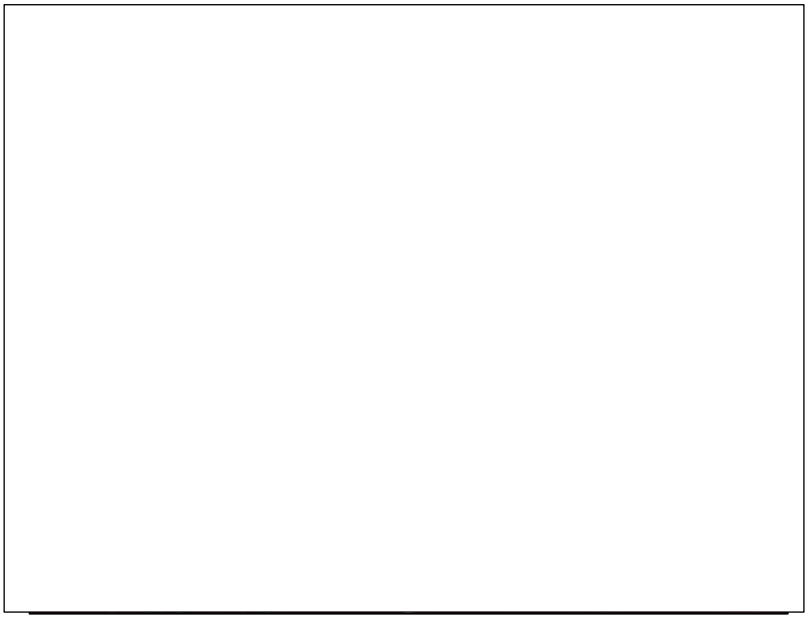


Figure 16: Mechanism of action of TC-325 - (A)Endoscopic targeting of the site of bleeding. (B)(C) TC-325 applied at the site of bleeding, water absorbed from the blood and a protective haemostatic barrier formed. (D) TC-325 shortens clotting times by concentrating clotting factors and blood cells. Courtesey of Barkun et al (151).

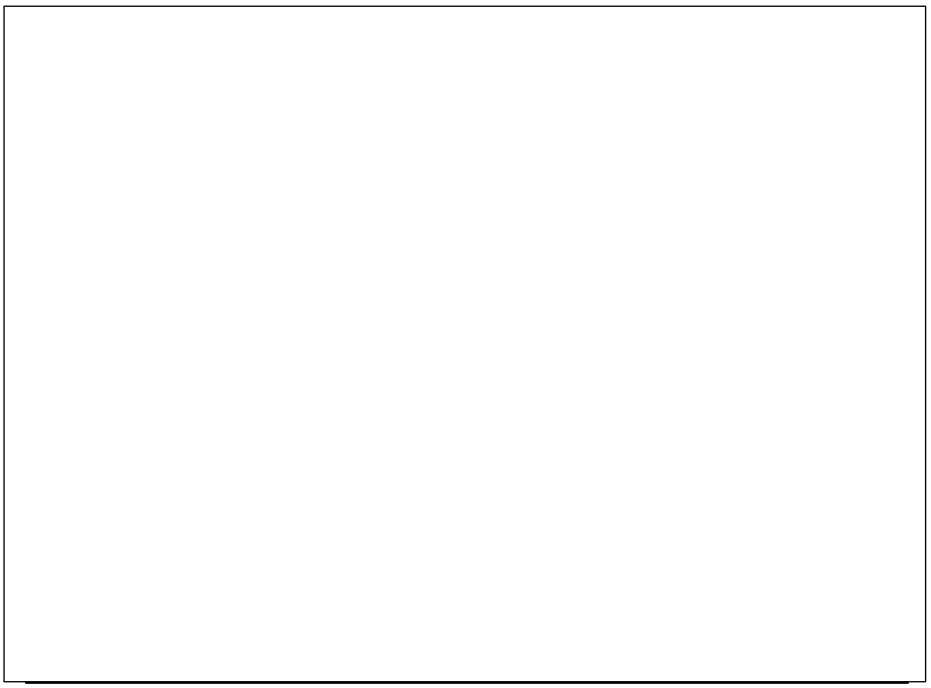


Figure 17: TC-325 powder is delivered through the catheter (1), (2) Powder cartridge, (3) activation knob, (4) Red security valve, (5) Trigger button. Image courtesy of Bustamante-Balen et al.(150)

1.3.4.2 Other haemostatic powders

Endoclot is a haemostatic powder which consists of absorbable modified polymers which are derived from plant starch. On contact with bleeding the polymer absorbs the water and as a result a gel matrix is formed and allows for concentration of coagulation factors(152). Bagel et al published a study assessing outcomes of the use of Endoclot. There was an immediate haemostasis rate of 76.5% in actively bleeding patients. There were no adverse events and one reported technical failure (153). A prospective multicentre study showed a 64% haemostasis rate following the use of Endoclot in upper GI bleeding and an 83% haemostasis rate in lower GI bleeding(154).

UI-EWD (Nexpowder) consists of succinic anhydride and oxidised dextran which becomes an adhesive hydrogel when in contact with moisture. This creates a mechanical barrier and allows for haemostasis following a GI bleed. It does not require active bleeding to activate which means it may play a potential role in prophylaxis following higher risk endoscopic procedures. A pilot study of 17 patients that failed conventional endoscopic therapy showed a haemostasis rate of 94% with nexpowder, and a re-bleeding rate of 19%(155).

Ankaferd blood stopper consists of herbal extracts from five different plants. When in contact with moisture an encapsulated protein network is created which then allows for erythrocyte aggregation and haemostasis. Studies have shown haemostasis rates ranging from 73% to 100% and re-bleed rates from 0% to 33%(156)(157)(158)(159)(152).

1.4 Thesis study aims

I present in this thesis a suite of five studies linked with the common theme of detection of early oesophageal cancer and treatment of associated GI bleeding complications. The first study is a retrospective analysis which shows the scale of the problems with detection of early dysplasia in Barrett's oesophagus. The studies in the following chapters will show the development of new artificial intelligence systems for the detection and characterisation of dysplasia and cancer in Barrett's oesophagus. The early cancer that is detected will need to be endoscopically treated which is associated with bleeding risks. There are also risks of bleeding with advanced oesophageal malignancy when not detected and treated early. The last two chapters will evaluate the efficacy and safety of a haemostatic powder for the management of Gastrointestinal bleeds secondary to endoscopic therapy in the oesophagus and for the treatment of more advanced oesophageal malignancy related bleeds.

STUDY 1: The natural history of low-grade dysplasia in Barrett's oesophagus and risk factors for progression to high grade dysplasia and oesophageal adenocarcinoma

1. To compare the risk of progression of true low-grade dysplasia in Barrett's oesophagus versus the cohort of patients downstaged from low grade dysplasia to indefinite for dysplasia/non dysplastic Barrett's oesophagus.

2. To assess the rates of upstaging of low-grade dysplasia to high grade dysplasia/oesophageal adenocarcinoma or downstaging of low-grade dysplasia to indefinite for dysplasia/non dysplastic Barrett's oesophagus following referral from district general hospitals to a tertiary centre where the histology is reviewed by expert Barrett's histopathologists.

3. To identify risk factors associated with the progression of true low-grade dysplasia to high grade dysplasia/oesophageal adenocarcinoma to help identify a higher risk cohort of patients with low grade dysplasia in Barrett's oesophagus that may have a higher benefit from endoscopic therapy.

STUDY 2 – The development of deep neural networks for the detection and localisation of dysplasia and neoplasia in Barrett's oesophagus and comparing the performance versus endoscopists

1- To develop a deep neural network to detect dysplasia in a segment of Barrett's oesophagus by:
    - Classifying a still image of a segment of Barrett's oesophagus as dysplastic or non-dysplastic.
    - After classifying an image to then be able to localise points of interest on an image
        - with targeted biopsy marks to guide endoscopists as to where to sample tissue from.
        - with delineations around areas of interest as an alternative technique of guiding endoscopists where to sample tissue from.

2- To achieve the above aims at high speeds to allow real-time detection of dysplasia

3- To compare the performance of the Artificial intelligence system on i-scan 1 versus white light imaging using the Pentax imaging system.

4- To compare the performance of the Artificial intelligence system with non-expert endoscopists

<u>STUDY 3</u> – The development of deep neural networks for the characterisation of dysplasia in Barrett's oesophagus on magnification imaging

1- To develop a computer aided diagnosis system that can diagnose dysplasia in Barrett's oesophagus on i-scan 3/optical enhancement magnification endoscopic imaging on three different levels:
    a. High quality still images – selected high quality frames to reflect the real-world decision-making process where endoscopists can freeze an image to make an assessment and diagnosis on magnification imaging.
    b. Short sequence of frames – continuous sequence of frames reflecting the real-world decision-making process where an endoscopist will make a decision based on a short assessment of a section of the oesophagus.

c. On whole videos of the oesophagus – assess the performance of the convolutional neural networks on all the available frames from the oesophagus. It may be more than one different location in the oesophagus which has been assessed. This would gauge the overall robustness of the model

2- Secondary aims were to assess the speed of the networks in diagnosing dysplasia and early cancer in Barrett's oesophagus on magnification endoscopy.

<u>STUDY 4</u> – Use of TC-325 for the management of bleeding following endoscopic therapy in the oesophagus

1- To assess the success of endoscopic haemostasis with TC-325 in patients with uncontrolled intraprocedural bleeding following endoscopic therapy in the oesophagus

2- Secondary aims included:
   a. To assess the 7 and 30-day rates of rebleeding following TC-325 treatment of intraprocedural bleeding following endoscopic therapy in the oesophagus
   b. To assess the 7 and 30-day mortality rate following the treatment of intraprocedural bleeding in the oesophagus with TC-325
   c. Compare the performance of TC-325 when used as a monotherapy, combination therapy or rescue therapy in the treatment of intraprocedural bleeding following endoscopic treatment in the oesophagus
   d. To assess for any adverse events following TC-325 treatment post endoscopic therapy in the oesophagus
   e. Compare the performance of TC-325 in the treatment of intraprocedural bleeding in the oesophagus to treatment of intraprocedural bleeding following endoscopic treatment in the stomach and duodenum

<u>STUDY 5</u> – Use of TC-325 for the management of upper gastrointestinal bleeding secondary to oesophageal cancer

1- To assess the immediate haemostasis rates following the treatment of oesophageal malignancy related GI bleeds with TC-325

2- Secondary aims were
    a. To assess the 30-day re-bleed rate following the treatment of oesophageal malignancy related bleeding with TC-325
    b. To assess the 30-day mortality rate following the treatment of oesophageal malignancy related bleeding with TC-325
    c. To compare the outcomes of patients with gastric or duodenal malignancy related bleeds versus oesophageal malignancy related bleeds treated with TC-325
    d. To assess the effect of TC-325 treatment on transfusion requirement in all sub cohort of patients

CHAPTER 2

THE NATURAL HISTORY OF LOW-GRADE DYSPLASIA IN BARRETT'S OESOPHAGUS AND RISK FACTORS FOR PROGRESSION TO HIGH GRADE DYSPLASIA AND OESOPHAGEAL ADENOCARCINOMA

CHAPTER 2 THE NATURAL HISTORY OF LOW-GRADE DYSPLASIA IN BARRETT'S OESOPHAGUS AND RISK FACTORS FOR PROGRESSION TO HIGH GRADE DYSPLASIA AND OESOPHAGEAL ADENOCARCINOMA

The work presented in this chapter formed the basis of a peer reviewed publication. Text and some of the figures were adapted for publication. Citation(160):

Hussein M, Sehgal V, Sami S, Bassett P, Sweis R, Graham D, Telese A, Jansen M, Novelli M, Banks M, Lovat L.B. and Haidry R, 2021. The natural history of low-grade dysplasia in Barrett's esophagus and risk factors for progression. Journal of Gastroenterology and Hepatology Open, 5 (9): 1019 – 1025.

2.1 Introduction

The study in this chapter sets the scene for showing the importance of early detection of dysplasia such that curative endoscopic therapy can be offered to patients. There is potentially early detection tools described in the studies in **chapters 3** and **4** that can help support early diagnosis of dysplasia. The work in this chapter shows that despite advances in endoscopic technology and despite analysis by histopathologists early dysplasia can be missed therefore risking progression to cancer.

Barrett's oesophagus (BO) is the only known risk factor for the development of oesophageal adenocarcinoma (OAC). There is a sequence of progression from non-dysplastic BO (NDBO), to low grade dysplasia (LGD), high grade dysplasia (HGD) and then OAC (161). OAC is known to be associated with approximately a less than 20% five-year survival rate (162).

Approximately 15-40% of all patients diagnosed with BO are also diagnosed with LGD at some point during their lifetime. LGD is a risk factor for progression to HGD and OAC therefore a clear management strategy for treating LGD is needed(163).

There has been a significant amount of controversy around the management of LGD in BO. This is due the variability in studies with regards to the natural history of LGD in BO and there is also a significant interobserver variation between histopathologists with regards to its diagnosis (164). International guidelines recommend expert histopathologist consensus with regards to the diagnosis of LGD in BO (7) (165).

A multicentre prospective study found that European pathologists diagnose fewer cases of LGD with predominant inflammatory features using fewer criteria for the definition of dysplasia compared with histopathologists from the USA. It is felt that this potentially could explain the higher rates of progression to HGD/OAC in European studies (166) (161). Several studies have shown that LGD is often over diagnosed. Duit et al analysed 293 patients diagnosed with LGD by pathologists based in the community. Following review by expert pathologists the initial diagnosis of LGD was confirmed in 27% of patients. 14% of patients were downstaged to indefinite for dysplasia (IND) and 59% to NDBE. In those with a confirmed diagnosis of LGD the rate of progression was 9.1% per patient-year compared to 0.6% per patient-year in patients who were downstaged to IND/NDBE (35) (167).

There is no international consensus with regards to the natural history of progression of LGD in BO to HGD/OAC. Some studies suggest a progression rate of 6% from LGD to HGD/OAC. In some studies, the LGD was confirmed by one histopathologist. This cannot be completely reliable as the LGD was not always reproduced on follow up endoscopies. The difficulty to confirm LGD again may be explained by the similar cytological features between dysplasia and inflammation related injury. It becomes difficult to differentiate between the two and as a result LGD may be over diagnosed in BO. Conio et al showed that in patients with a diagnosis of LGD at index endoscopy, this was not confirmed in 75% of cases on further surveillance endoscopies (168)(169) .

Variable progression rates have been reported of LGD ranging from 0.4 – 13.4% per year(170). A randomised study showed a high rate of progression in a surveillance cohort of patients with LGD in BO (26.4% progressed to HGD/OAC)(49). A systematic review showed that the cumulative rate of progression to HGD/OAC was lower in the cohort of patients that were treated with radiofrequency ablation compared to the surveillance cohort (1.7% versus 12.6%, $P < 0.001$) (170). Many of the studies did not involve expert BO histopathologists which may explain some of these variations.

As well as lack of histological consensus there is also a lack of consensus with regards to the management of LGD in BO. The American College of Gastroenterology (ACG) recommends endoscopic therapy even if surveillance is indicated. The European Society of Gastrointestinal endoscopy (ESGE) guidelines suggest endoscopic therapy after a diagnosis is confirmed by an

expert pathologist after a 6-month surveillance interval. The American Society of Gastrointestinal Endoscopy (ASGE) guidelines recommend endoscopic therapy of LGD after a confirmed diagnosis on a repeat endoscopy 6 months after the index endoscopy with LGD (165) (171) (172).

There has been a variation between studies with regards to the risk factors associated with progression of LGD in BO. Wani et al in a study of 210 patients with LGD in BO found that were no risk factors for progression and also found significant interobserver variation in the diagnosis of LGD even amongst expert histopathologists (173). Song et al found that persistent confirmed LGD was an independent risk factor for progression to HGD/OAC. Confirmed LGD was defined as LGD which was confirmed by consensus from expert histopathologists. Persistent LGD was defined as LGD identified again on a follow up endoscopy procedure. This group felt persistent LGD would be a useful marker in determining the management of BO (174).

Validating risk factors for progression of LGD may help with regards to patient selection in terms of those that receive treatment with Radiofrequency ablation particularly in view of the variability in the diagnosis of LGD amongst expert histopathologists. For example, patients with confirmed LGD where there is a higher rate of progression.

2.2 Aims of this study

There were three main aims to the study in this chapter:

1- To compare the risk of progression of patients with confirmed true LGD versus the cohort of patients downstaged from LGD to IND/NDBO

2- To assess the rates of upstaging of LGD to HGD/OAC or downstaging of LGD to IND/NDBO following referral from district general hospitals to a tertiary centre where the histology is reviewed by expert BO histopathologists

3- To identify risk factors associated with the progression of confirmed LGD to HGD/OAC to help identify a higher risk cohort of patients with LGD in BO that may have more benefit from endoscopic therapy.

2.3 Definitions

These are the main definitions of outcomes and terms used within this chapter:

1. True LGD (T-LGD): LGD confirmed on index endoscopy following referral and reviewed by two expert Barrett's histopathologists.

2. Downstaged LGD to NDBO (DS-LGD-NDBO): LGD downstaged to NDBE following referral and reviewed by two expert Barrett's histopathologists.

3. Downstaged LGD to IND (DS-LGD-IND): LGD downstaged to IND following referral and reviewed by two expert Barrett's histopathologists

4. Unifocal LGD: LGD present on one biopsy level within a segment of BO following Seattle protocol biopsies.

5. Multifocal LGD: LGD present on more than one biopsy level within a segment of BO following Seattle protocol biopsies.

2.4 Methods

2.4.1 Patient recruitment

I performed a retrospective cohort analysis of all consecutive BO LGD referrals in a single tertiary centre (University College London Hospital, UCLH) (July 2006 – October 2018). All patients underwent high-definition white light endoscopy with chromoendoscopy at baseline with targeted and Seattle protocol biopsies following referral. All biopsies were reviewed by at least two expert Barrett's histopathologists with more than 10 years of BO pathology experience following which the diagnosis was either downstaged to NDBO/IND, remained the same (confirmed LGD) or upstaged to HGD/OAC. Any visible lesions/nodularity at baseline were endoscopically resected, and histology reviewed.

2.4.2 Inclusion and exclusion criteria

The inclusion criteria for the study were:

-All patients who meet the standard definition of BO and have LGD within BO on biopsies

-All pathology slides were reviewed by at least two expert Barrett's histopathologists from index endoscopies following referral.

-Patients did not receive endoscopic eradication therapy prior to referral and had at least one follow-up endoscopy post index procedure with biopsies at the tertiary centre

-There is no history of HGD/OAC in BO

Exclusion criteria for the study were:

-Patients with a history of HGD/OAC in BO

-Following index endoscopy following referral to the tertiary centre if the pathology slides were not reviewed by expert BO histopathologists.

-If patients had a prior history of endoscopic eradication therapy prior to the tertiary referral.

2.4.3 Primary and secondary outcomes

Confirmed and eligible LGD patients were offered endoscopic eradication therapy. A number preferred active surveillance and were monitored. Progression time was defined as the time from the first endoscopy following referral to date of progression to HGD/OAC.

The primary outcome was time to progression to HGD/OAC. Secondary outcomes were risk factors for progression of LGD to HGD/OAC and rates of upstaging/downstaging of LGD following referral to IND or NDBO.

2.5 Statistical analysis

The first analysis summarised the pathological staging of patient following review by an expert histopathologist. Patients were classified as either downstaged, no staging change (ie confirmed LGD) or upstaged. Descriptive statistics were used to summarise results.

In patients who were not upstaged time to progression was examined. As not all patients progressed, survival analysis methods were used. Progression time was defined as the time from the index endoscopy following referral to the tertiary centre to date of progression to HGD/OAC. Patients who did not progress were censored at the time of last known follow-up. Some patients

had no follow-up time beyond the initial index endoscopy following referral and were therefore excluded from the analysis.

Factors associated with the time to progression were analysed. The analysis for this outcome was performed using cox regression. Firstly, the separate association between each factor and the time to progression was examined using univariable analyses. The second stage in the analyses considered the joint association between factors and the outcomes in a multivariable analysis. To restrict the number of variables in this second stage of analysis, only variables showing some association with the outcomes in the univariable analyses ($p \leq 0.2$) were included.

2.6 Results

2.6.1 Baseline data

A total of 164 patients with a diagnosis of low-grade dysplasia in BO were assessed. A total of 147 patients had a diagnosis of LGD in BO that met the inclusion/exclusion criteria for this study and included in the analysis. 17 patients were excluded. The median age of patients included in the analysis was 71 (IQR, 64-77) and 86% were male.

133 patients were external tertiary referrals. 42 (32% of patients) of the referred patients had their diagnosis upstaged to HGD following their index endoscopy and review by two histopathologists, 49 (37% of patients) patients had their diagnosis downstaged to NDBO (n=31) or IND (n=18), and 42 (32% of patients) patients had the same confirmed LGD diagnosis (Figure 18).

In the confirmed LGD group a median number of 14 biopsies were taken per patient (Interquartile range, 11-20 biopsies). In the group downstaged to IND/NDBO a median number of 14 biopsies were taken per patient (Interquartile range, 8-20 biopsies).

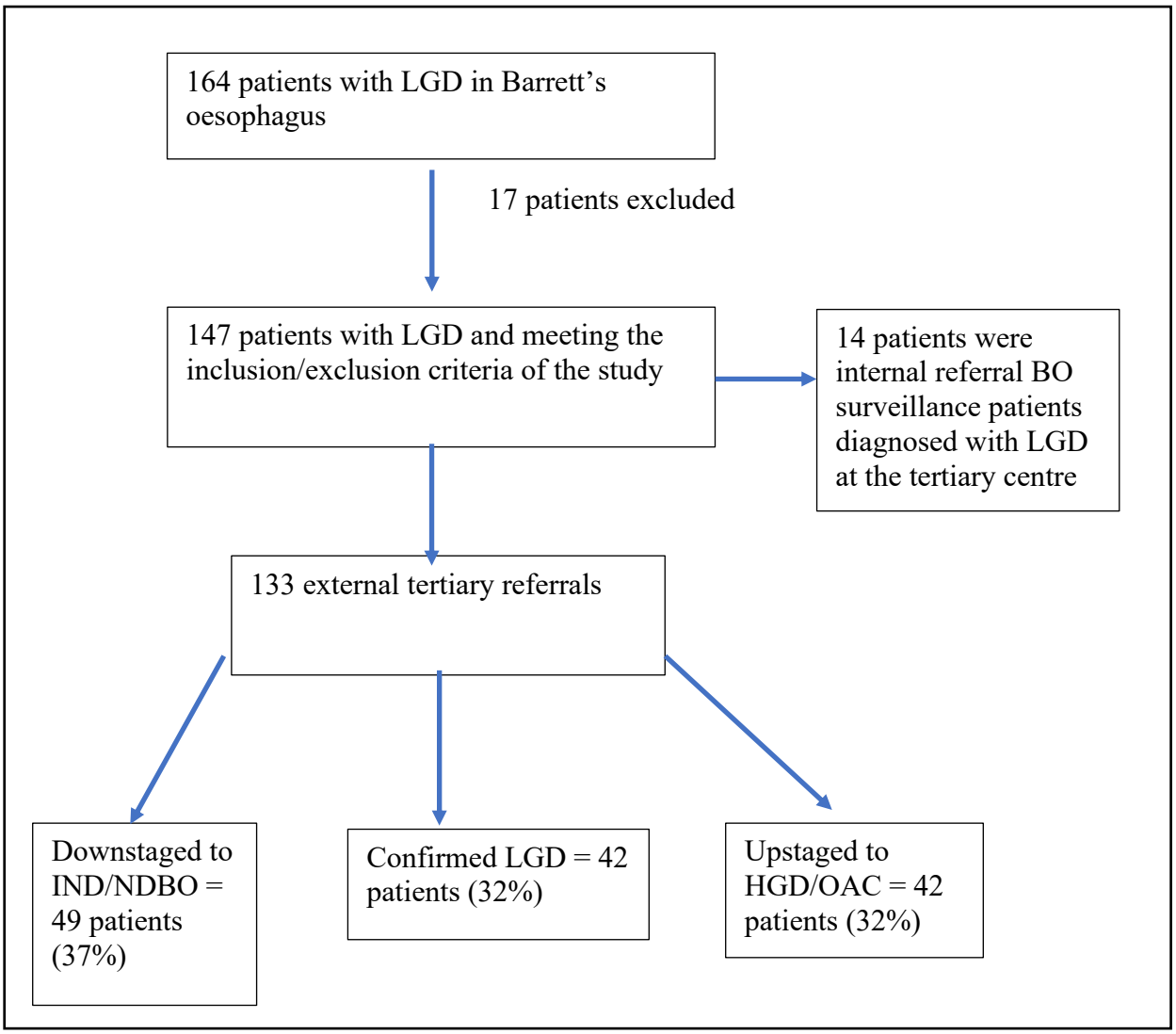


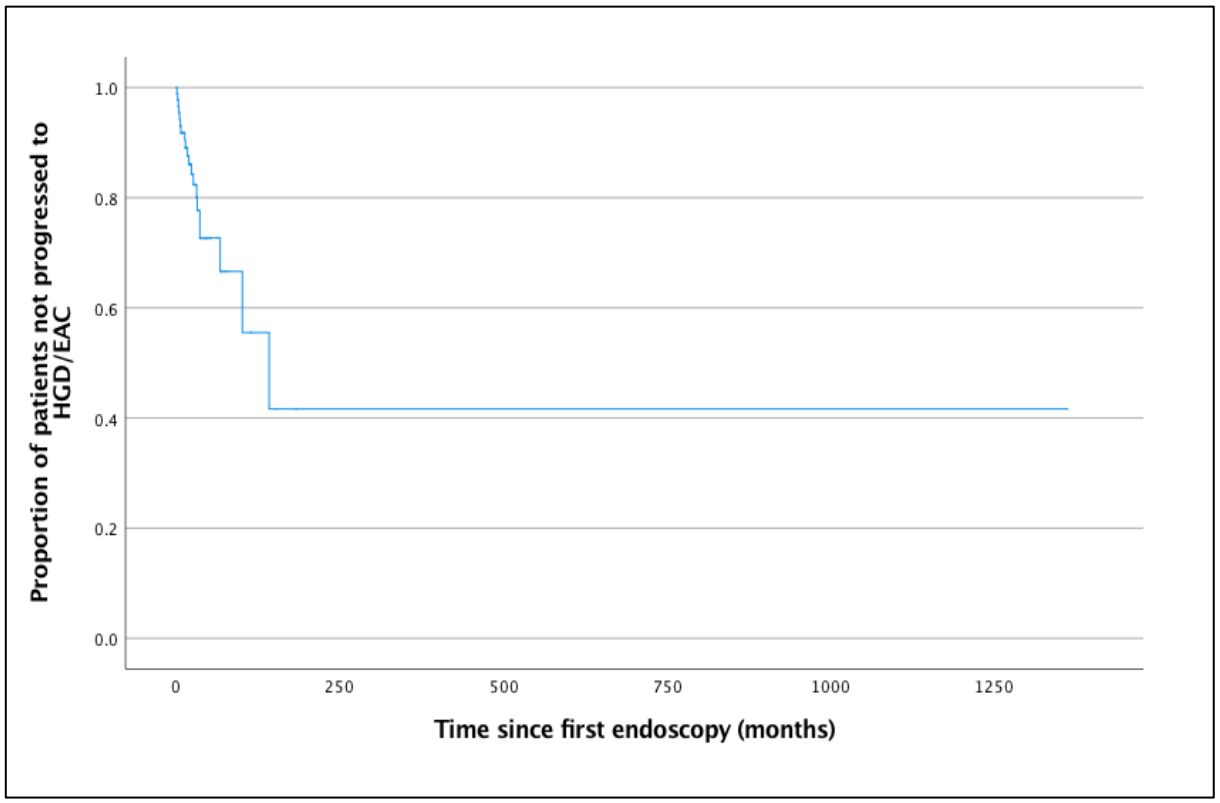
Figure 18: Histology results of Barrett's oesophagus biopsies following tertiary referral as low-grade dysplasia and review of histology by expert Barrett's histopathologists

2.6.2 Time to progression to high grade dysplasia/Oesophageal adenocarcinoma

The next analysis examined the time to progression in patients that were not upstaged. For the survival analysis I omitted the patients that were upstaged at referral (42 patients) and patients that had one index endoscopy at the tertiary centre with no follow up biopsies (14 patients). This left 91 patients, of these 20 (22% of patients) patients progressed during the follow up period (Figure 19).

73% of patients had not progressed at 5 years. 58% had not progressed at 10 years. The median time to progression was 11.8 years (95% CI: 4.6 years to 19.1 years).

Figure 19: Time to progression of HGD/OAC of all 91 patients that had follow up endoscopies with biopsies after their index endoscopy (T-LGD, DS-LGD-NDBO, DS-LGD-IND). Time 0 represents the start of the follow up period.



2.6.3 Risk factors for the progression of low grade dysplasia to high grade dysplasia/oesophageal adenocarcinoma

Analyses were performed to examine the factors associated with time to progression in the T-LGD cohort (n=56) (Table 4). 6 patients had no follow up endoscopy and were therefore excluded from this part of the analysis (n = 50). Univariable analysis showed nodularity in BO on index endoscopy and the location of low-grade dysplasia (unifocal versus multifocal) was significantly associated with time to progression when each factor was considered separately ($P < 0.05$). Patients with nodularity at baseline endoscopy had an increased chance of progression despite endoscopic resection with risk of progression at any time being almost 4 times greater than patients with no evidence of nodularity on index endoscopy (Hazard ratio 3.56 (1.13,11.27), P =0.03). Patients with multifocal LGD had an almost 5 times greater risk of progression compared to patients with unifocal LGD (Hazard ratio 4.82 (1.33, 17.54) P=0.02). Patient age, gender, the presence of a hiatus hernia on endoscopy, the length of the BO segment and smoking status do not seem have a significant impact on the time to progression based on this analysis.

Multivariable analysis suggested some evidence that nodularity at index endoscopy, location of low-grade dysplasia (unifocal versus multifocal) and endoscopic therapy were associated with time to progression (Table 5). Patients undergoing endoscopic therapy had a three times lower risk of progression compared to patient who never underwent endoscopic therapy and just undertook surveillance follow up endoscopies and monitoring. After adjusting for therapy, the risk of progression at any time was six times higher for patients with nodularity at index endoscopy compared to patients without, whilst the risk of progression was almost four times higher in multifocal LGD compared to unifocal LGD.

Table 4: Univariable analysis of the time to progression of T-LGD to HGD/OAC

Variable		Progression	Hazard ratio (95% CI)	P- value
Age (**)	-	-	1.00 (0.96, 1.04)	0.99
Gender	Female	1/4	1	0.98
	Male	13/46	1.03 (0.13, 7.97)	
Nodularity	No	9/39	1	**0.03**
	Yes	5/11	3.56 (1.13, 11.27)	
Location	Unifocal LGD	3/25	1	**0.02**
	Multifocal LGD	11/23	4.82 (1.33, 17.54)	
Hiatus hernia (HH)	No	6/22	1	0.83
	Yes	8/28	0.89 (0.31, 2.59)	
HH size (+)	Small (<3cm)	5/13	1	0.60
	Large (>3cm)	3/15	0.68 (0.16, 2.88)	
Length (C) (*)	-	-	1.01 (0.90, 1.15)	0.82
Length (M) (*)	-	-	0.98 (0.85, 1.14)	0.83
Smoking status	Non-smoker	7/21	1	0.72
	Current smoker	1/7	1.35 (0.28, 6.49)	
	Ex-smoker	2/7	0.58 (0.05, 6.47)	
PPI medication	No	1/3	1	0.50
	Yes	12/40	2.04 (0.26, 16.19)	
Endoscopic therapy during follow up and after referral	No	11/33	1	0.09
	Yes	3/17	0.32 (0.09, 1.18)	

(*) Hazard ratios given for a 1-unit increase in variable

(**) Hazard ratios given for a 1-unit increase in variable

(+) Analysis for patients with hiatus hernia only

Table 5: Multivariable analysis of time to progression of T-LGD to HGD/OAC

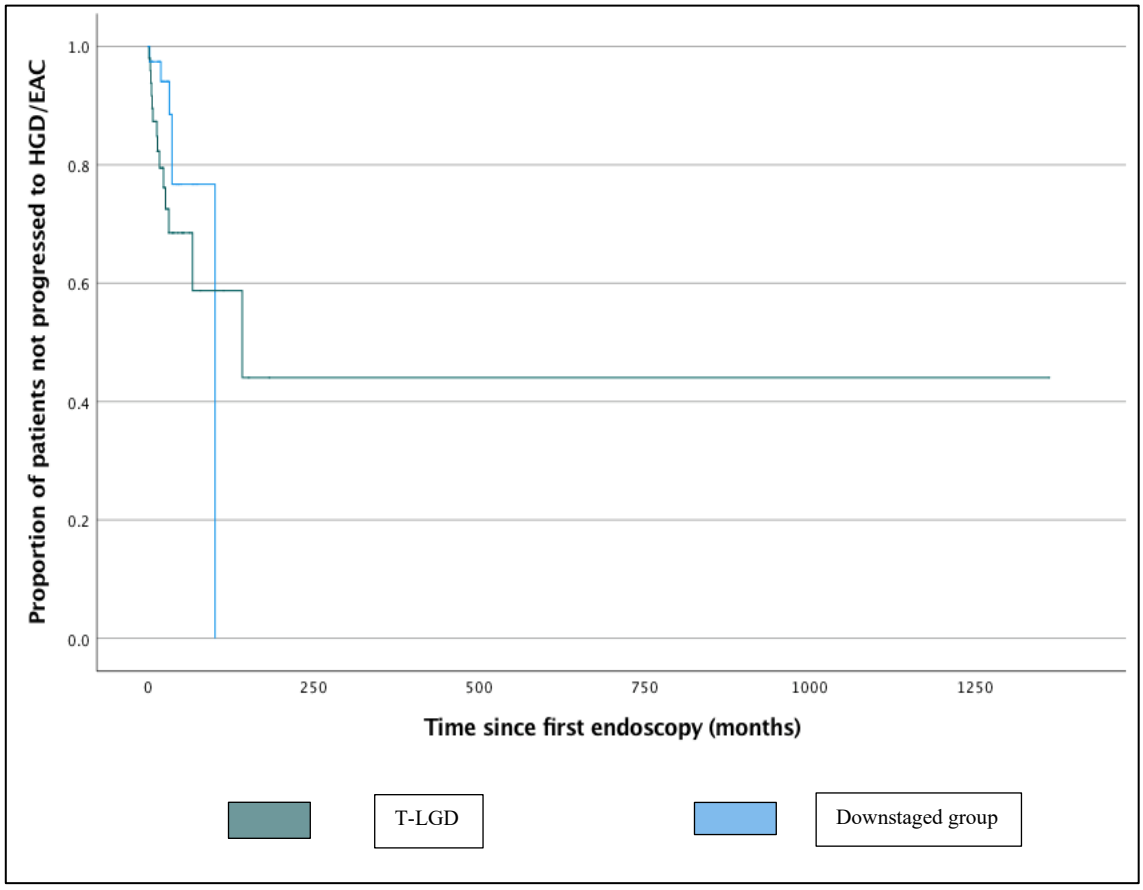
Variable	Category	Hazard ratio (95% CI)	P-value
Nodularity at index endoscopy	No	1	0.007
	Yes	5.54 (1.60, 19.17)	
Location of dysplasia	Unifocal LGD	1	0.05
	Multifocal LGD	3.78 (0.98, 14.59)	
Endoscopic therapy	No	1	0.09
	Yes	0.31 (0.08, 1.22)	

T-LGD = True low-grade dysplasia; HGD = high grade dysplasia; OAC = Oesophageal adenocarcinoma

2.6.4 Comparison of the true low grade versus the down staged cohort

69% of patients in the T-LGD cohort had not progressed to HGD/OAC at 5 years. Overall, 14 out of 50 patients with T-LGD progressed to HGD/OAC. 77% of patients in the DS-LGD-NDBO/DS-LGD-IND cohort did not progress to HGD/OAC at 5 years. 6 out of 41 patients with DS-LGD-NDBO/DS-LGD-IND progressed overall. There was no significant difference in time to progression between patients with T-LGD and those that were downstaged to IND/NDBO (P = 0.21) (Figure 20).

Figure 20: Kaplan-meier plot showing time to progression of T-LGD (n=50) versus DS-LGD-NDBO/DS-LGD-IND (N=41)) to high grade dysplasia/oesophageal adenocarcinoma. There was no significant difference (P=0.21). Time 0 represents the start of the follow up period.



T-LGD = True low-grade dysplasia; NDBO = non dysplastic Barrett's oesophagus; IND = Indefinite for dysplasia

2.6.5 Natural history of progression of patients with confirmed low-grade dysplasia in Barrett's oesophagus

33 patients had T-LGD diagnosed by two expert histopathologists and no prospective history of ablation therapy. 59% of these patients had not progressed to HGD/OAC at 5 years. Overall, 11 out of 33 patients progressed to HGD/OAC. The median time to progression was 67 months (95% confidence interval: 3 to 131) (Table 6).

15 patients were downgraded to IND and had no prospective history of ablation therapy treatment. 78% of these patients had not progressed to HGD/OAC at 5 years. 2 out of 15 patients overall progressed to HGD/OAC. 20 patients were downgraded to NDBO and had no prospective history of ablation therapy. 74% of these patients had not progressed to HGD/OAC at 5 years. 3 out of 20 patients progressed overall to HGD/OAC.

The overall median time to progression in these three cohorts was 101 months (95% Confidence interval: 52 to 150). There was no significant difference in the time to progression between the three cohorts (P=0.22).

Table 6: Natural history of progression of Barrett's oesophagus with true low-grade dysplasia in patients with no history of ablation therapy

	T-LGD (N =33)	**(DS-LGD-IND) (n =15)**	**DS-LGD-NDBE (N = 20)**
Mean age, years	72	71	71
Male sex	31/33 (94%)	13/15 (87%)	16/20 (80%)
Proportion of patients that have not progressed at 5 years	59%	78%	74%
Number of patients progressing to HGD/OAC	11	2	3

T-LGD = True low-grade dysplasia; DS-LGD-IND = Low grade dysplasia downstaged to indefinite for dysplasia; DS-LGD-NDBE = Low grade dysplasia downstaged to non-dysplastic Barrett's oesophagus

2.7 Discussion

It is known that dysplasia in BO is associated with an increased risk of progression to OAC/HGD. Guidance regarding the management of OAC/HGD in BO is clear in terms of offering endoscopic eradication therapy as a first line treatment(174) (165). The management of patients with LGD can include either surveillance endoscopies with biopsies or endoscopic eradication therapy. A particular issue is the variation in the diagnosis of LGD by histopathologists which can contribute to concerns in offering endoscopic therapy given the potential risks that can be associated with these procedures.

The SURF study showed that 12% of patients developed a stricture after radiofrequency ablation (RFA) requiring endoscopic dilatation and three serious adverse events were observed(49). There were no adverse events in the surveillance cohort. Therefore, careful consideration should be taken weighing up the risks and benefits prior to offering endoscopic treatment even though radiofrequency ablation treatment is overall a safe and effective procedure. It is extremely important that an accurate diagnosis is made of LGD in BO from the outset. We need to not over treat this patient cohort and try and minimise interobserver variability of its diagnosis.

In this study there is variability in the diagnosis of LGD from referring centres. Only a third of all patients had confirmed LGD following review by two expert histopathologists. 32% of patients were upstaged to HGD and a third of patients were downstaged to no dysplasia or indefinite for dysplasia and continued surveillance endoscopies with biopsies. This re-affirms the importance of the requirement of a diagnosis of LGD to be reviewed and confirmed by two expert pathologists at an expert and high-volume Barrett's centre. A study found excellent concordance between histopathologists in the diagnosis of HGD and NDBO (>70%), however intermediate agreement for LGD amongst 51 pathologists (42%)(175). A study found that 73% of patients with LGD in BO had their diagnosis downstaged to NDBO/IND and they had a lower risk of progression compared to the T-LGD cohort(35).

The cumulative incidence of progression to HGD/OAC and time to progression varied across subgroups. The T-LGD cohort of patients had double the rates of progression compared to the downstaged cohort. At 5 years 59% of the T-LGD cohort of patients had not progressed versus 78% and 74% in the DS-LGD-IND and DS-LGD-NDBO cohort respectively. This suggest that this is a particularly high-risk cohort of patients with a higher risk of progression over a shorter period. It is important to differentiate the patient subgroups. Decisions on surveillance and endoscopic treatments can be more personalised, and resources utilised more wisely. A previous study of 147 patients diagnosed with LGD showed that patients with T-LGD had a cumulative risk of progressing of 85% in 109.1 months, relative to 4.6% in 107.4 months for the DS-LGD-NDBO/DS-LGD-IND cohort(36).

5 out of 35 patients in the ablation naïve cohort who were downstaged to NDBO/IND progressed to HGD/OAC. This is a smaller proportion compared to 11 out of 33 patients that progressed in the true LGD cohort. The proportion of patients that progressed in the downstaged cohort was higher than a previous study where the 5 year cumulative risk of progression was 2.9% and 2.1% in the downstaged IND and NDBO cohort(35). This reflects the variability in the diagnosis of LGD and these 5 patients in our study may have been downstaged but may have had true LGD. The other important reason for this difference may have been that there was a smaller number of patients in the ablation naïve cohorts in study discussed in this chapter therefore it would be difficult to do a direct comparison. Given the risk of progression in the downstaged cohort an argument can be made for ablation treatment in this cohort however this does carry risks and most patients in this group do not progress. An alternative would be an adjusted shorter

surveillance interval for these group of patients who do not carry the same progression risk as the true low-grade patients. An alternative strategy would be increasing the number of pathologists reviewing the histology slides of patients with low grade dysplasia.

In my study patients with LGD that had ablative therapy had a three times lower risk of progression relative to patients who were followed up with long term surveillance biopsies. The long-term outcomes of a randomised control trial showed that radiofrequency ablation in LGD significantly reduces the risk of progression after a median follow up of 73 months. This study affirms the importance in offering endoscopic therapy to the T-LGD cohort. They are a particularly higher risk cohort. A study found that patients with LGD in BO that were treated with ablation reported a quality of life comparable with patients undergoing endoscopic surveillance (176). In my study patients received either radiofrequency ablation, cryoablation or argon plasma coagulation therapy.

33 patients had T-LGD and no ablation history allowing us to analyse their natural history. 70% of patients were diagnosed prior to the updated 2015 British Society of Gastroenterology (BSG) guidelines. At that point the recommendation for LGD in BO was a repeat endoscopy every 6 months.

A study carried out an analysis from three population-based models showing the optimal management for patients with LGD in BO is endoscopic eradication therapy only after LGD is confirmed(177). These are findings confirmed in the study in this chapter where all patients had a second endoscopy to confirm LGD given the variability in its diagnosis with a reduction in rates of progression in patients receiving ablation therapy. This allows therapy to be focused on the T-LGD patients (38% of the overall patient cohort).

The two main risk factors for progression in the cohort of patients I studied was the presence of nodularity at index endoscopy and multifocal LGD ($P < 0.05$). If the nodularity was unifocal or multifocal did not influence outcomes. 95% of all patients that progressed were male. Age, gender, Barrett's length and smoking history were not associated with risk of progression. There have been variations in risks for progression in different studies. A multicentre prospective registry study showed that the risk of progression to HGD/OAC was eight-fold higher in the patient cohort where two expert GI pathologists re-confirmed a diagnosis of LGD. Another multicentre study showed that there were no risk factors for progression with significant

interobserver variation in diagnosis amongst expert pathologists(173). A single centre retrospective study of 69 patients showed that persistent LGD was an independent risk factor for progression to HGD/OAC(174). Khan *et al* showed that the length of BO was associated with a risk of progression(178). Identifying key risk factors of progression would potentially allow the building of a risk stratification tool which will help tailor treatment in a specific, higher risk cohort particularly when considering the potential associated risks with therapeutic interventions.

2.8 Study limitations and potential for future work

There are some limitations to the study. This is a single centre study and data collection was done retrospectively. The results would ideally be validated with a prospective multicentre study. Including multiple centres would allow generalisability of the results. Ideally pathological diagnostic inclusion criteria would be standardised across all centres to minimise interobservor variability in the diagnosis of LGD particularly in different countries.

In future work I will include an increased variability of pathologists to review histopathology slides to reach a consensus regarding the diagnosis of low-grade dysplasia. This will allow me to investigate the variability in diagnosis and further confirm the difficulty in diagnosing these cohort of patients where there needs to be greater consensus in pathological criteria for diagnosis. There may be further variation in the number of patients downstaged to IND/NDBO and number of patients with T-LGD.

In future work I would include an analysis of P53 in all patients. I would assess whether this supports the confirmation of true LGD. As discussed in chapter 1 (section 1.1.8.1) P53 has been shown to improve the interobservor agreement between histopathologists in the diagnosis of dysplasia compared to a histopathologists assessment alone. I would also assess whether P53 helps in risk stratifying the risks of progression of these patients. Therefore, if it would support weighing up the risks and benefits of offering endoscopic therapy to a specific cohort of patients with a higher progression risk. Januszewicz et al showed with the inclusion of P53 immunohistochemistry there was a more than 40% reduction in the diagnosis of indefinite for dysplasia in Barrett's oesophagus, therefore reclassifying it to definitive dysplasia(79).

A combination of P53 overexpression combined with risk factors such as multifocal LGD and nodularity at index endoscopy could potentially help risk stratify these findings. A large multicentre study of Barrett's tertiary centres can be done to validate these risk factors and create a scoring system that can be potentially useful in the clinical setting.

The outcome of my study suggests there needs to be more stringent pathological criteria for the diagnosis of LGD in BO in the community. The T-LGD cohort are a higher risk cohort, and these patients need to be identified and if fit should undergo endoscopic therapy following patient discussion. Certain variables can be used to identify those much higher risk patients. The presence of nodularity at index endoscopy and multifocal LGD seems to be associated with higher progression rates. A risk stratification tool will help identify high-risk LGD patients that require endoscopic eradication therapy.

2.9 The potential role of Artificial intelligence in the diagnosis of low-grade dysplasia

AI is a central theme in this thesis. This may potentially play an important future role in helping better diagnose low grade dysplasia. AI can have a role in automating the diagnosis of LGD histopathology on pathology slides and minimise interobservor variation between pathologists. There is also a potential role for AI in diagnosing dysplasia and then characterising LGD real time using magnification endoscopic imaging. This is much more difficult to do than in the characterisation of OAC and HGD and requires large volumes of data to train a system to do this accurately. In **Chapter 3** we demonstrate a novel AI system which can detect all grades of dysplasia in BO including LGD during endoscopic assessment of Barrett's oesophagus.

A pooled analysis of multicentre analysis studies showed an automated tissues system pathology test may have an important role in predicting the risk of progression in patients with BO without dysplasia or with evidence of LGD(179). This will support the personalised treatment approach for patients. Patients can be better risk stratified, and the higher risk patients can be offered endoscopic therapy.

2.10 Summary of the chapter

In this chapter I have looked at the risk of progression of confirmed LGD to OAC/HGD and the risk factors for progression.

1. I have showed that there is a variability in the diagnosis of LGD. Approximately a third of patients were upstaged to HGD, a third downstaged and therefore only a third of all tertiary referrals had confirmed and true LGD.

2. I have showed that patients with true LGD in BO have higher rates of progression compared to the downstaged patients therefore representing a higher risk cohort of patients where endoscopic therapy should potentially be focused. This reflects the importance of making an accurate diagnosis to help risk stratify these patients and help support with decisions regarding endoscopic treatment.

3. I have demonstrated that patients with confirmed LGD that had ablation therapy had a lower risk of progression relative to patients that did not have ablative therapy.

4. I have demonstrated that the presence of nodularity at index endoscopy within the BO segment and the presence of multifocal LGD are associated with a significant risk of progression to HGD/OAC. Therefore, patients with these features can potentially be deemed to be higher risk.

5. There is a need for tools such as Artificial intelligence systems to help support the confirmation of diagnosis of LGD in BO and help risk stratify patients and their risk of progression. This will allow for a more personalised management on a case-by-case basis. This process may also reduce the need for a repeat endoscopy every 6 months or two confirmed endoscopies with biopsies in keeping with LGD. This may lead to a scenario where only one endoscopy is required, and treatment can be offered at an earlier stage if needed. This will reduce costs, minimise unnecessary endoscopies and better streamline the patient pathway.

CHAPTER 3

THE DEVELOPMENT OF DEEP NEURAL NETWORKS FOR THE DETECTION AND LOCALISATION OF DYSPLASIA AND NEOPLASIA IN BARRETT'S OESOPHAGUS AND COMPARING THE PERFORMANCE VERSUS ENDOSCOPISTS

CHAPTER 3 THE DEVELOPMENT OF DEEP NEURAL NETWORKS FOR THE DETECTION AND LOCALISATION OF DYSPLASIA AND NEOPLASIA IN BARRETT'S OESOPHAGUS AND COMPARING THE PERFORMANCE VERSUS ENDOSCOPISTS

The work presented in this chapter formed the basis of a peer reviewed publication. Text and some of the figures were adapted for publication. Citation(127):

Hussein M, Gonzalez-Bueno Puyal J, Lines D, Sehgal V, Toth D, Ahmad OF, Kader R, Everson M, Lipman G, Ortiz Fernandez-Sordo J, Ragunath K, Esteban JM, Bisschops R, Banks M, Haefner M, Mountney P, Stoyanov D, Lovat LB and Haidry R. A new artificial intelligence system successfully detects and localised early neoplasia in Barrett's esophagus by using convolutional neural networks. United European Gastroenterol J 2022; 10 (6): 528 – 537.

3.1 Introduction

As previously discussed in Chapter 1 in the introduction to this thesis BO is associated with an increased risk of progression to LGD, HGD and then OAC. Early detection is key to minimise the risk of progression and to then be able to offer the appropriate curative endoscopic treatment early. The overall five year survival of OAC is less than 20% (162). If early cancer in BO is treated with curative endoscopic eradication therapy the survival rates of these patients is more than 90% (116). As discussed, following the analysis in chapter 2 certain types of dysplasia such as LGD in BO are more difficult to detect. I found in that study that there was a variability in the diagnosis of LGD which is often upstaged or downstaged following central review by two histopathologists in a high-volume Barrett's centre. Those with true confirmed LGD were a relatively higher risk cohort with a greater risk of progression to cancer.

The current standard practice in the endoscopic assessment of BO is to take quadrantic biopsies every two cm as part of the Seattle protocol biopsies. The disadvantages of this established technique are that it is time consuming, there is poor compliance(112) and sampling error(116) with interobserver variability in measurements. Also, another issue is that despite the advances in endoscopic imaging technology over the last decade a significant proportion of early cancers in BO can still be missed particularly in non-expert centres which do not have regular BO surveillance lists. A meta-analysis showed that amongst patients with NDBO at index

endoscopy, 25% of the missed oesophageal adenocarcinomas are diagnosed within a year of the index procedure(82).

Studies on early detection of lesions in the Gastrointestinal tract have largely focused on the detection and characterisation of colonic polyps(180). There are very few studies on the detection of dysplasia in BO (123) (124). AI can potentially have a major impact on our clinical practice as a supportive adjunct to endoscopists which reduces the number of random biopsies during BO surveillance, therefore lowering histopathology costs, with shorter procedure times which could potentially improve the quality and comfort of the procedure for patients. With the support of AI more cancers can be potentially identified earlier, and endoscopic therapy can be offered which would offset the costs of an oesophagectomy or radiotherapy if cancer is missed and therefore progresses. AI can potentially support a shorter procedure time particularly if it is able to allow us to take a more targeted biopsy approach rather than the larger number of biopsies associated with the Seattle Protocol. This would allow for more procedures to be done on a list which is particularly important in the context of the COVID-19 pandemic associated backlog due to the reduction in routine endoscopic provision that was associated with it. This resulted in huge waiting lists which all endoscopy units in the United Kingdom have to get through (59).

With advances in endoscopic imaging and optical technology classification protocols have been generated on different endoscopic systems based on the mucosal pit pattern and the vascular architecture to improve the detection of BO dysplasia (181) (97)(96). These are the same features one would train a computer aided detection system to carry out the same task.

I-scan (Pentax Hoya, Japan) is a virtual chromoendoscopy technique which uses a post processing technology to provide both surface and contrast enhancement. There are 3 different modes embedded into this technology - i-scan 1 (Surface enhancement), i-scan 2 (contrast enhancement), i-scan 3 (tone enhancement). The AI algorithm discussed in this chapter has been developed using this imaging system. To the best of my knowledge no studies have previously developed a neural network exclusively using the Pentax i-scan imaging system prior to this study. Therefore, this would provide a novel contribution to the field of Gastroenterology. Previous studies have developed neural networks of detection of dysplasia in BO with some encouraging results mainly using the Fuji and Olympus imaging systems (122) (125). I-scan 1 is the best imaging mode for detection of early cancer on the Pentax-imaging system. It has therefore become the default imaging modality, and I reflect this in my work in this chapter to

try and mimic potential real world implementations for these systems. Previous research has shown that using optical enhancement with i-scan is superior to White light in BO assessment. This has paved the way for i-scan to be first line standard of care in most units using the Pentax imaging system(96).

Many of the studies to date have trained neural networks using limited high-quality data from limited centres which means there would potentially be a lack of generalisability in such models. This may have an impact of running these systems in real time in the endoscopy unit in different centres across the world which would be the goal.

In this chapter I demonstrate experiments for developing a neural network for the detection of early cancer in Barrett's oesophagus. A couple of different methodologies will be demonstrated in developing a network before deciding on a final methodology which reflects real world practice and gives reasonable performance outcomes. I also demonstrate a comparison of the performance of the AI system versus experienced non expert endoscopist in the detection of dysplasia in BO to try and show whether it would provide any benefit to human endoscopists and the potential impact this could have on real world practice.

3.2 Aims of the study

The overall focus of the study in this chapter were to develop a robust AI system that can aid endoscopists with the early detection of dysplasia and early neoplasia during a BO surveillance assessment. There were three main aims to this chapter:

- To develop a deep neural network to detect dysplasia in a segment of BO by:
    - Classifying a still image of a segment of BO as dysplastic or non-dysplastic.
    - After classifying an image to then be able to localise points of interest on an image:
        i. with targeted biopsy marks to guide endoscopists as to where to sample tissue from.
        ii. with delineations around areas of interest as an alternative technique of guiding endoscopists where to sample tissue from.

- To achieve the above aims at high speeds to allow real-time detection of dysplasia

- To compare the performance of the AI system on i-scan 1 versus white light imaging

- To compare the performance of the AI system versus non expert endoscopists

3.3 Initial feasibility study for the development of a neural network to classify for the presence of dysplasia in Barrett's oesophagus

This section will discuss the initial experiment that was performed to develop a neural network which can classify the presence or absence of dysplasia in BO. At the time of performing this experiment the area of AI and BO was a novel area and there were not many strategies to base the analysis and model development on. This chapter will reflect the initial strategy used to develop a classifier and how this then went on to lead to my main study in the next section within this chapter (section 3.4). The chapter will then focus on how we developed a separate algorithm using a segmentation model for the localisation of dysplasia in BO.

3.3.1 Methods

3.3.1.1 Recruitment of patients

Patients attending for BO assessment at two expert European centres were recruited (London and Leuven). Most cases were recruited from a single centre as part of this feasibility study. A limited number of cases were included in this initial experiment. As this was the initial pilot study a decision was made to include most cases that were from a single centre and add in a small number of cases from external hospitals. All cases were collected prospectively including cases collected as part of a previous BO imaging study using the same standard protocol of endoscopic assessment (Figure 21 and Figure 22). Patients were excluded if there were oesophageal strictures, oesophageal varices or oesophageal ulceration. The study was approved by the Cambridge central research ethics committee (REC reference No. 18/EE/0148) for UK site. The European centre received ethical approval from their local committee for use of images for this and other imaging-based research projects.

3.3.1.2 Endoscopic assessment and collection of videos

Six expert endoscopists were involved in performing the procedures where the videos were collected as part of this study. These were defined as endoscopists with more than 5 years' experience with performing BO endoscopic therapy and perform such procedures weekly in BO centres as defined by the European Society of Gastrointestinal Endoscopy (ESGE) guidelines(56).

All videos were collected prospectively using the Pentax endoscopy system (EPK-i7000, OPTIVISTA plus, EG-29990i, EG29-i10). Mucus lining the oesophagus was cleaned using a simethicone and water solution. Endoscopists performed a 'pull through' withdrawal of the endoscope from the gastroesophageal junction to the maximal extent of BO. Procedures were all recorded in high-definition white light and i-scan 1 imaging modes in patients with NDBO and patients with dysplastic lesion in BO (HGD/OAC). I-scan 1 was the default imaging modality used in all centres.

I identified and booked any potential Barrett's oesophagus cases that met the inclusion/exclusion criteria on to the relevant list. I ensured the endoscopist followed the steps for pull through (Figure 15 and 16) to ensure a standardised approach was followed. I downloaded the video data immediately after each case and allocated an anonymised code name for each case. I ensured that the data on the videos were anonymised using an anonymisation tool. For video data collected retrospectively from previous studies I assessed each video to ensure they met the inclusion/exclusion criteria for the study. I also allocated a code name for each of these cases.

I collected the relevant metadata for each video which included the following information:

- Imaging modality available on the video – White light, I-scan 1, I-scan 2, Iscan-3/optical enhancement
- Histology on the video case
    - Non dysplastic Barrett's oesophagus
    - If dysplastic Barret's oesophagus, then if the histology was:
        - Low grade dysplasia
        - High grade dysplasia
        - Intramucosal adenocarcinoma
- Presence or absence of a visible lesion

- Difficulty of detection of a lesion by a non-expert endoscopist – mild, moderate or difficult. The difficulty was graded by me.
- The Paris classification of the lesion
- Presence/absence of a cap on the endoscope
- Hospital/country where data was collected from
- Date case was recorded

Figure 21: Step by step process of pull back recordings during endoscopy in non-dysplastic Barrett's oesophagus

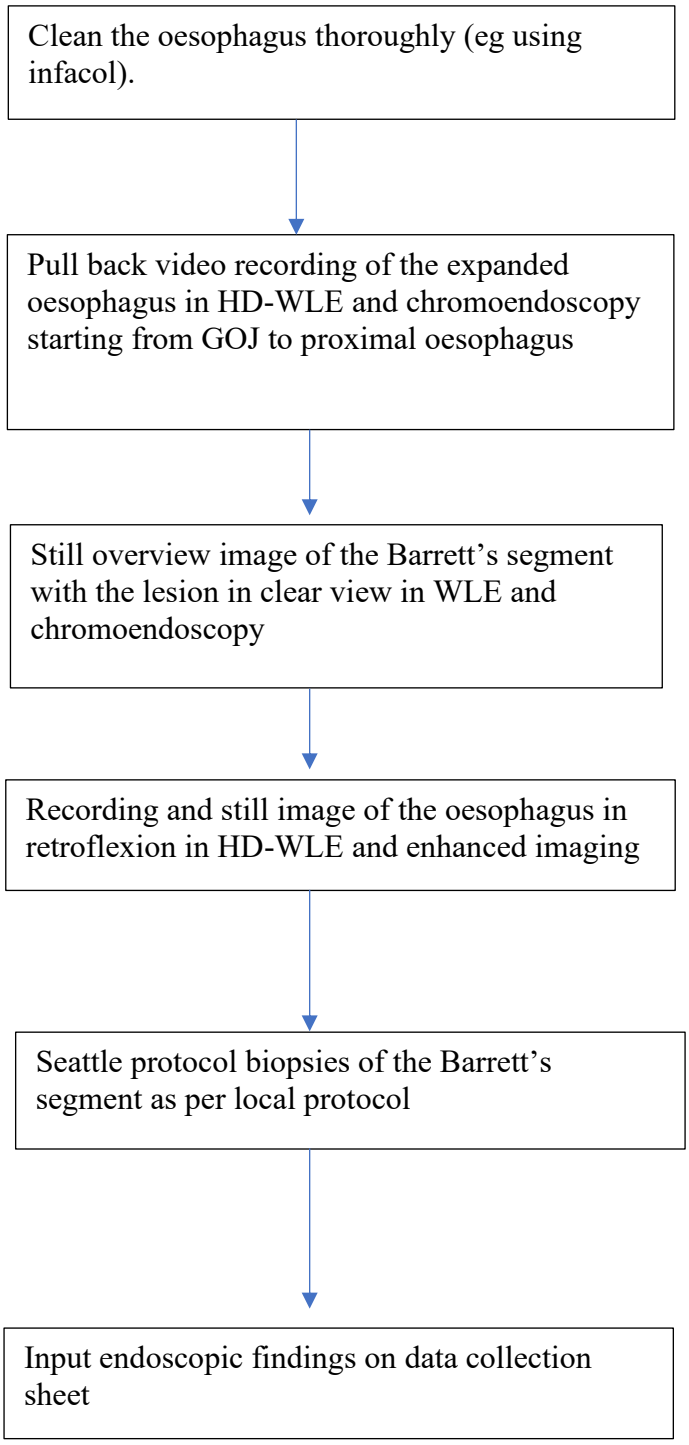
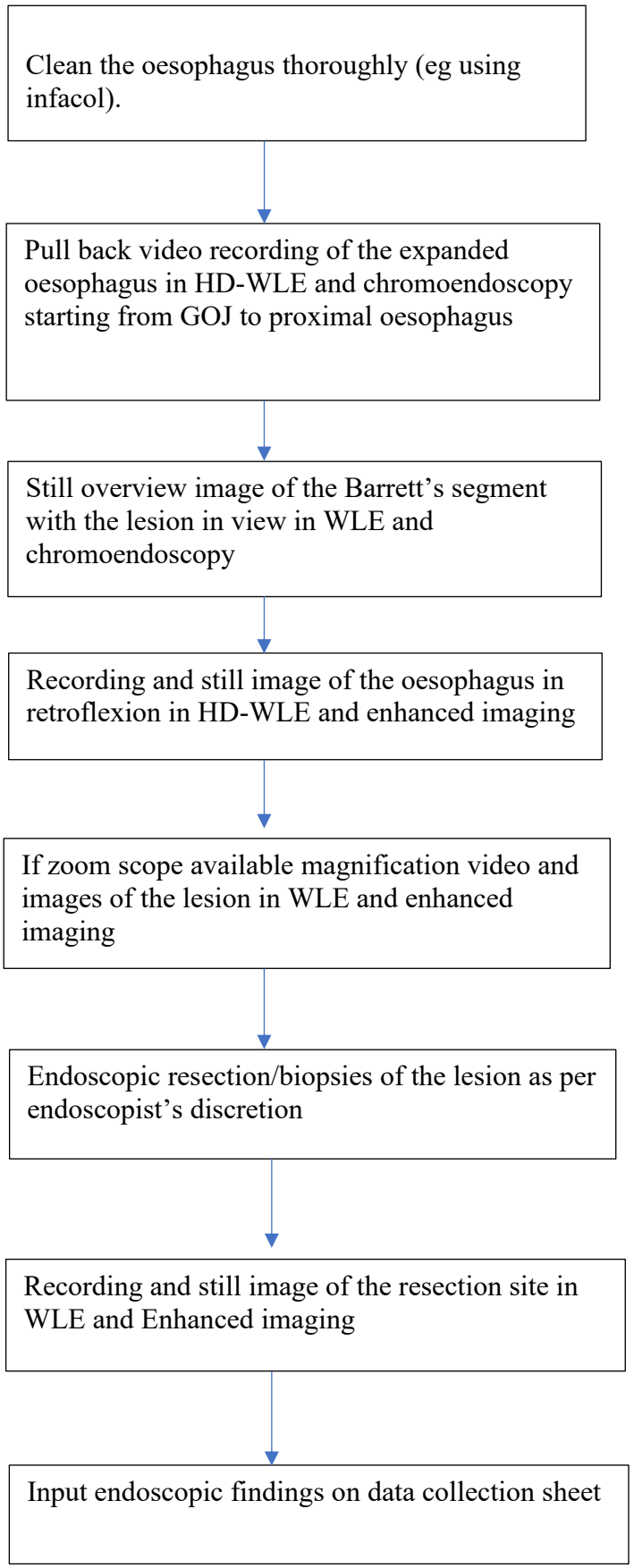


Figure 22: Step by step process of pull back recordings during endoscopy in Barrett's oesophagus with lesion/dysplasia



3.3.1.3 Tissues acquisition and histology

During the assessment of BO during an endoscopic 'pull through' if there was no suspicion of dysplasia the whole area was biopsied as per the Seattle protocol and standard of care. Any areas that were suspicious for dysplasia were either target biopsied or resected by endoscopic mucosal resection if appropriate. All histology was reviewed by expert BO histopathologists in their respective centres with more than 10 years of experience.

3.3.1.4 Creation of a gold standard on video segments

A computer vision annotation tool (Odin Vision, London, UK) was used to annotate a sequence of video frames. All videos where there was evidence of dysplasia were annotated for the definite presence of dysplasia. These annotations were extracted as XML files from the annotation tool. They formed part of the dysplasia group. Videos that did not contain dysplasia were not specifically annotated for 'no dysplasia' in this experiment and these videos formed part of the control group. The dysplastic frames and the whole non dysplastic videos were used to train and validate a classification convolutional neural network.

I defined this as an indirectly supervised learning approach. Most studies on AI and BO trained networks based on delineations of lesions on individual still images performed by experts. In this case we train the networks using whole areas of videos with or without dysplasia. The network works out what is defined as an abnormality within the frames for itself.

3.3.1.5 The classification convolutional neural network for the detection of dysplasia within Barrett's oesophagus

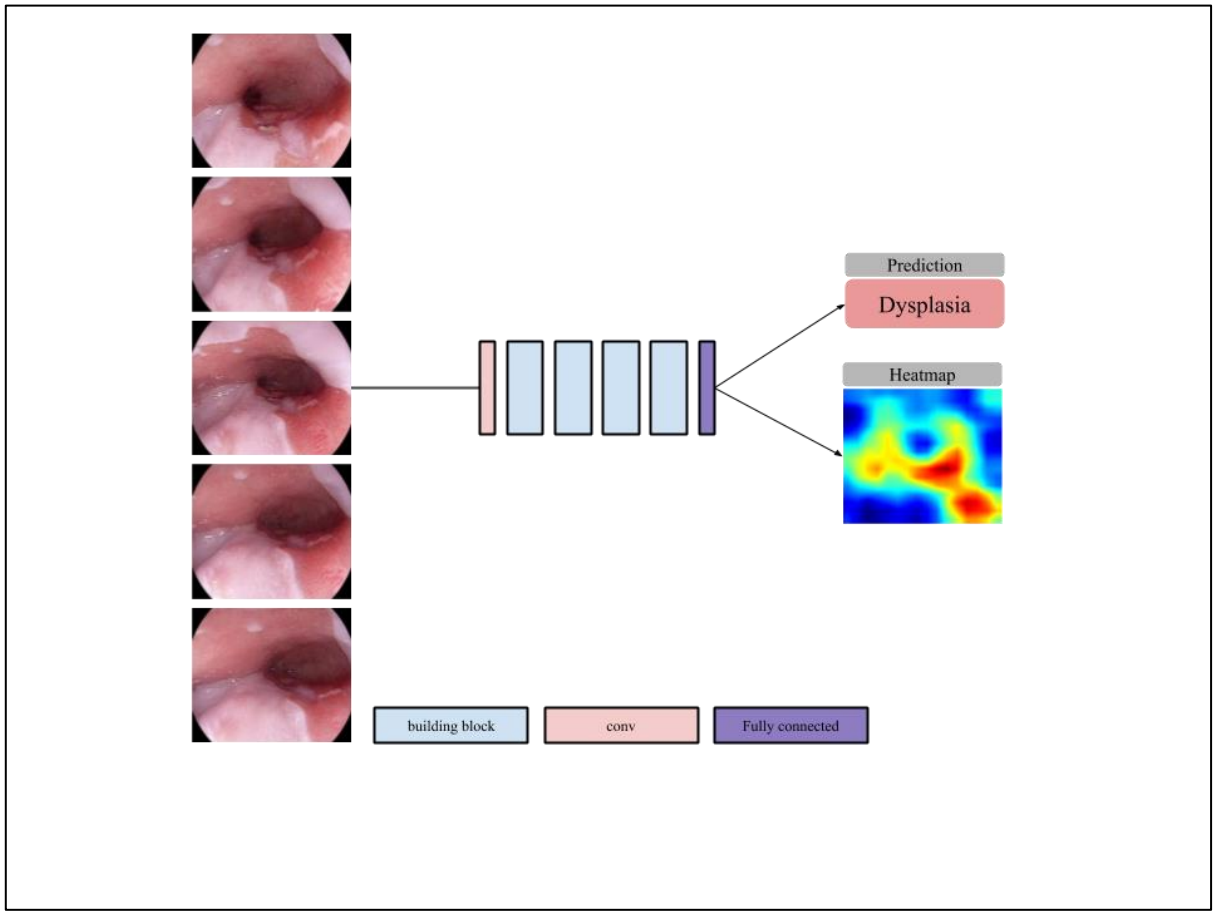
We trained a convolutional neural network with a Resnet101 architecture to classify images into dysplastic or non-dysplastic using randomly selected frames from annotated videos (Figure 23).

As explained in the introduction chapter a residual network (Resnet) is a convolutional neural network (CNN) which is designed to allow the training of very deep and efficient networks. A Resnet101 architecture is a type of model hyperparameter which defines the architecture of the model. It is a CNN which has 101 layers.

For each pixel, the CNN would predict a number between 0 (no dysplasia) and 1 (dysplasia present). Temporal filtering was used which computes the prediction of frame as the average over a certain number of previous consecutive frames.

The data set was trained, tested and validated on all the different imaging modalities (White light, i-scan 1, i-scan 2 and i-scan 3/optical enhancement).

Figure 23: CNN structure and output for the detection of dysplasia in Barrett's oesophagus(127)



CNN: Convolutional neural network

3.3.2 Results

65 patients were included (28 patients with HGD/OAC and 37 patients with NDBO). A total of 266,930 frames were included in the study. The cases were randomly split into three independent groups with no overlap of data or patients: training (N =39 patients, 17 with dysplasia, 22 without dysplasia), validation set (N = 7 patients, 3 with dysplasia, 4 without dysplasia) and a testing set (N = 19 patients, 8 with dysplasia and 11 without dysplasia) (Figure 24). Table 7 shows the breakdown of the data based on histology and location

Table 7: Summary of the breakdown of the dataset in the training, testing and validation set based on location and histology

	Location		Histology		
	London	Leuven	NDBO	HGD	IMC
Training set	37/39 (95%)	2/39 (5%)	22/39 (56%)	10/39 (26%)	7/39 (18%)
Testing set	19/19 (100%)	0/19	11/19 (58%)	5/19 (26%)	3/19 (16%)
Validation set	7/7 (100%)	0/ 7	4/7 (57%)	3/7 (43%)	0/7

NDBO = non dysplastic Barrett's oesophagus; HGD = high grade dysplasia; IMC = intramucosal adenocarcinoma

For training, a balanced data set was created with equal numbers of dysplastic and non-dysplastic frames. All the available dysplastic frames were included. The non-dysplastic frames were chosen randomly to match the number of dysplastic frames as whole videos of BO assessments of areas of NDBO were included and were not specifically annotated. The CNN was trained using a total of 73,266 frames. This was then validated on a balanced validation set of 4228 frames.

The test set included 189, 436 frames (9194 with dysplasia). Temporal filtering was used which computes the prediction of frame as the average over a certain number of previous consecutive frames. A dysplastic lesion was diagnosed if it was presence in a sequence of 49 consecutive frame.

The decision or classification threshold was set at 0.25. The decision threshold is the threshold which determines how the model classifies an output into dysplasia or no dysplasia. Changing the value of the threshold adjusts the behaviour of the classifier. Different thresholds are chosen and then the outputs are analysed at these different thresholds and the one with the optimal output is chosen for the final model.

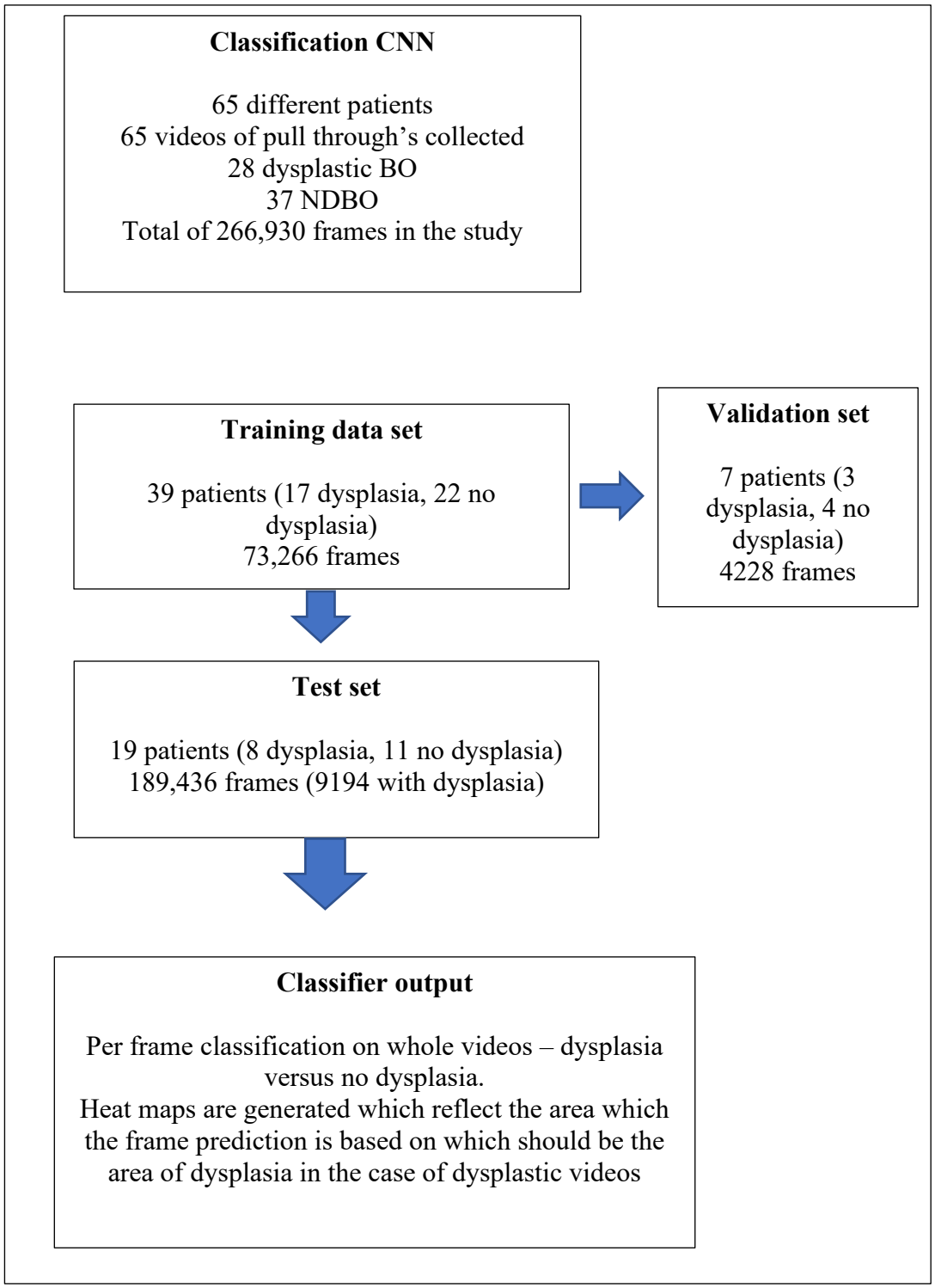
The CNN classified dysplasia in BO with:

- Sensitivity of 88.26%
- Specificity of 80.13%
- Area under the curve was 0.91 (Figure 25)
- Decision threshold = 0.25

- Temporal filtering used over 49 frames

Table 8 summarises calculations of the accuracy, sensitivity and specificity using different combinations of decision thresholds and temporal filtering using different numbers of frames ranging from zero to 49. The results that were described in this section were from experiment 22 from table 8 which gave the optimal performance and results.

Figure 24: Breakdown of the data set within the model to generate the classifier CNN



CNN = Convolutional neural network, NDBO = Non dysplastic Barrett's oesophagus

Figure 25: Area under the curve analysis for the CNN detection of dysplasia in video frames

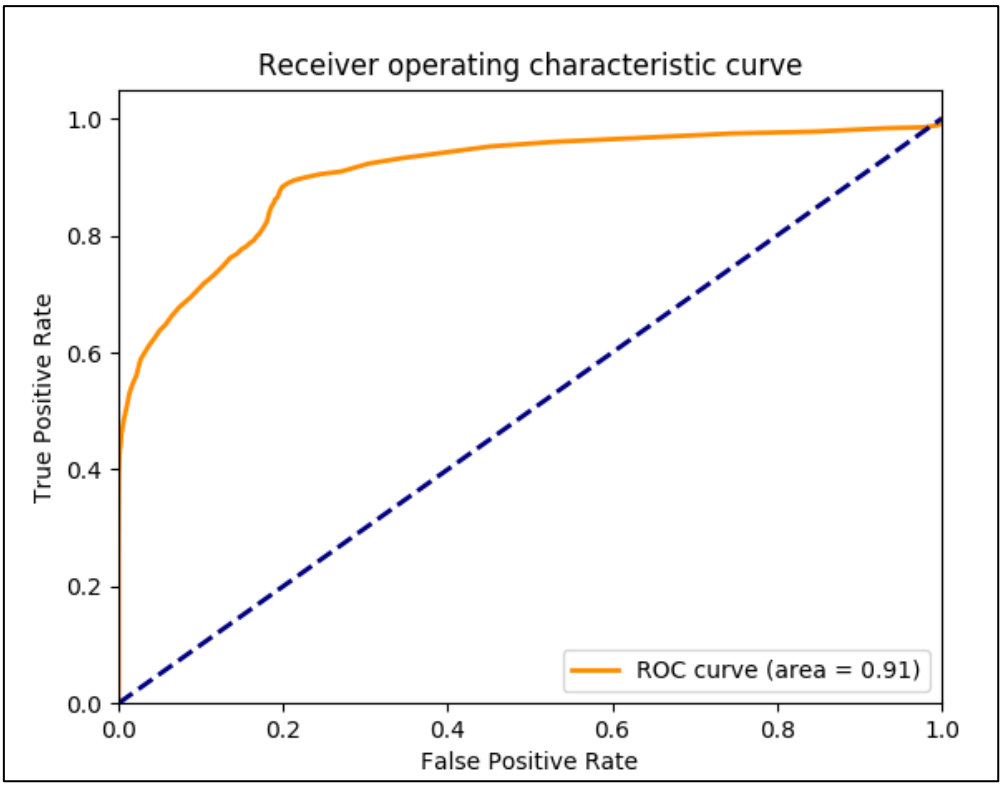


Table 8: Summary of accuracies, sensitivities and specificities generated using different combination of decision thresholds and temporal filtering using the data splits in this feasibility study. Experiment 22 gave the optimal results.

Experiment	Decision threshold	Temporal filtering (Number of frames)	Accuracy	Sensitivity	Specificity
1	0.5	No temporal filtering	0.84938	0.63661	0.86024
2	0.5	3	0.89165	0.63716	0.90463
3	0.5	5	0.90261	0.64466	0.91577
4	0.5	9	0.90881	0.65238	0.92189
5	0.5	15	0.91145	0.65619	0.92447
6	0.5	17	0.91197	0.66087	0.92478
7	0.5	20	0.92448	0.64705	0.93863
8	0.5	25	0.91417	0.67337	0.92645
9	0.4	No temporal filtering	0.79429	0.74538	0.79679
10	0.4	9	0.86571	0.76789	0.87070
11	0.4	12	0.88137	0.75266	0.88793
12	0.4	15	0.86149	0.77007	0.86615
13	0.4	17	0.86036	0.77333	0.86480
14	0.4	20	0.86967	0.76487	0.87502
15	0.4	25	0.85536	0.77627	0.85940
16	0.35	No temporal filtering	0.75579	0.79139	0.75398
17	0.35	5	0.82914	0.80444	0.83040
18	0.35	10	0.85974	0.79617	0.86298
19	0.35	15	0.83822	0.80683	0.83982
20	0.35	20	0.84368	0.80400	0.84570
21	0.35	25	0.83336	0.80958	0.83457
22	**0.25**	**49**	**0.80524**	**0.88258**	**0.80128**

3.3.3 Conclusion of the feasibility experiment

Preliminary data from this initial feasibility experiment showed that a convolutional neural network can be trained to detect dysplasia in BO with accuracies like endoscopists. The algorithm on this experiment was created using whole video frames which minimised selection bias.

3.3.4 Strategies that were changed based on the feasibility classification experiment

I made several observations from the initial experiment in section 3.3 to allow for improvements for the main experiment in this chapter described in section 3.4. I felt that these changes would reflect real world practices, would be more reproducible and generate better results going forwards. The main changes made were:

- Whole videos of non-dysplastic Barrett's oesophagus were originally included. Following inspection of this data set a lot of the videos were long and included a lot of frames with artefact. They also included parts of the stomach when assessing the distal aspect of the Barrett's oesophagus segment. This would potentially contribute to false positives. I made a decision to annotate the segments of the videos that included the oesophagus only in the non-dysplastic videos for the main experiment. The videos with dysplasia already had specific whole frame annotations as part of the feasibility study.
- The diagnosis of dysplasia in Barrett's oesophagus is difficult which is why there is a significant miss rate in non-expert centres. I made a decision to increase the size of the data set from a wider variety of centres to increase the generalisability of the model for the main experiment.
- We currently have a model which identifies dysplasia on a per image level. To make a new model more clinically relevant there was a need for targeted biopsy predictions. To do this there was a need for a segmentation model as part of the main experiment trained on expert delineations of areas of dysplasia
- For the current experiment the data set was trained, tested and validated on all the different imaging modalities (White light, i-scan 1, i-scan 2 and i-scan 3/optical enhancement). There was a need to test on specific imaging modalities which are more relevant to real world practice during the initial assessment of Barrett's oesophagus during a 'pull through' of the oesophagus. This would normally be done

with white light and/or i-scan 1 when using the Pentax imaging system. Therefore, a plan was made to generate a testing set using these imaging modalities only.

- The data for this initial experiment was largely from a single centre. I decided to increase the data set from 4 centres and include a larger volume of data to try and improve the strength of the results and make the models more generalisable.
- As discussed in Chapter 2 there is difficulty in diagnosing LGD in BO. I decided there was a need to include LGD in our testing set to assess the models performance on this.

3.4 Main Experiment– The development of neural networks which can successfully detect and localise early neoplasia in Barrett's oesophagus

3.4.1 Methods

3.4.1.1 Patient recruitment

Patients attending for assessment of BO were recruited from four European centres (London, Nottingham, Leuven and Madrid). All cases were collected prospectively including 86 that were collected prospectively as part of previous BO studies. Patients were excluded if there were oesophageal varices, ulceration or strictures. The study was approved by the Cambridge central research ethics committee (REC Reference No. 18/EE/0148). European centres received ethical approval from local committees for use of images for this and other imaging-based research projects

3.4.1.2 Endoscopic procedures and video collection

All videos were collected by six expert endoscopists involved in supporting the data collection for the study across all European centre's. An expert BO endoscopists was defined based on the same principals defined by the ESGE guidelines which is an endoscopist with more than 5 years of experience in BO endoscopic therapy and also performs these procedures weekly (171).

All videos were collected using the Pentax endoscopy system (EPK-i7000, EG-2990i, EG29-i10, OPTIVISTA plus). The oesophagus was first cleaned using a simethicone and water solution to provide optimal endoscopic views of the BO mucosa. The endoscopist then performed a 'pull through' withdrawal of the endoscope starting from the gastroesophageal junction to the maximum extent of BO. I-scan 1 was the default imaging modality in all centres. Pull throughs were recorded with HD-WL and I-scan 1 in dysplastic and NDBO cases. I-scan 2 and I-scan 3/optical enhancement pull throughs were also recorded as part of the case if the endoscopists performed this as part of standard of care to assess an area of abnormality in more detail.

3.4.1.3 Tissue acquisition and histology

If there were no suspicious areas of dysplasia on endoscopy the BO segment was biopsied as per Seattle protocol. If there were any areas suspicious for dysplasia these were either target biopsied or an EMR was performed. Histology was then be reviewed by expert BO histopathologists with at least 10 years of experience. If any cases were diagnosed as dysplastic, they were reviewed by two different BO histopathologists.

3.4.1.4 Creation of a gold standard on video segments

A computer vision annotation tool (Odin Vision, London, UK) was used to annotate video frames. Annotations would confirm that whole sequence of video frames within a 'pull through' video contained dysplasia without defining the exact position of the dysplastic area. The gold standard was the histology of the EMR specimens or the targeted biopsy histology. These always matched with the annotated areas on the videos.

In the cases with videos of NDBO all the video frames with the oesophagus only (including squamous islands) were annotated and included to form part of the training set. This differs from the original methodology in section 3.3 where whole NDBO videos were included which had the potential of creating lots of false positives with the data set including stomach as well.

Both the non-dysplastic and dysplastic video frames were used to train and validate a CNN.

3.4.1.5 Creation of a gold standard on still images

High and moderate quality BO images were extracted from videos by the same clinician on the study team. Figure 26 shows examples of what were considered high, moderate and poor-quality frames. These were defined in the following way:

High quality image = images with a clear view of the lesion within a distended oesophagus with no artefact (mucus and blood)

Moderate quality image = images which contain some artefact however the views of the lesion are of a reasonable quality to be able to make a diagnosis

Poor quality images = images with no clear views of the lesion. A positive or negative diagnosis cannot be made

These images were then delineated for dysplasia using the computer vision annotation tool by three BO expert endoscopists (Figure 27). Each image was delineated by two different endoscopists. All delineated areas were confirmed as dysplastic based on EMR or targeted biopsy histology results of the same area. These delineations were then used to test the performance of the CNN for localising a dysplastic area. The performance of the target biopsy prediction of the CNN was tested on two levels (Figure 28):

- The ability of the CNN to localise a targeted prediction of the dysplastic area that falls within any area annotated by either of the two experts on an image
- The ability of the CNN to localise a targeted prediction of the dysplastic area that falls within the small area of overlap between the two experts on each image.

These images also served the purpose of training a separate segmentation algorithm CNN which will more accurately help localise the areas of dysplasia on the image (Section 3.4.1.7).

Figure 26: Examples of what was considered high (A), moderate (B) and low (C) quality images

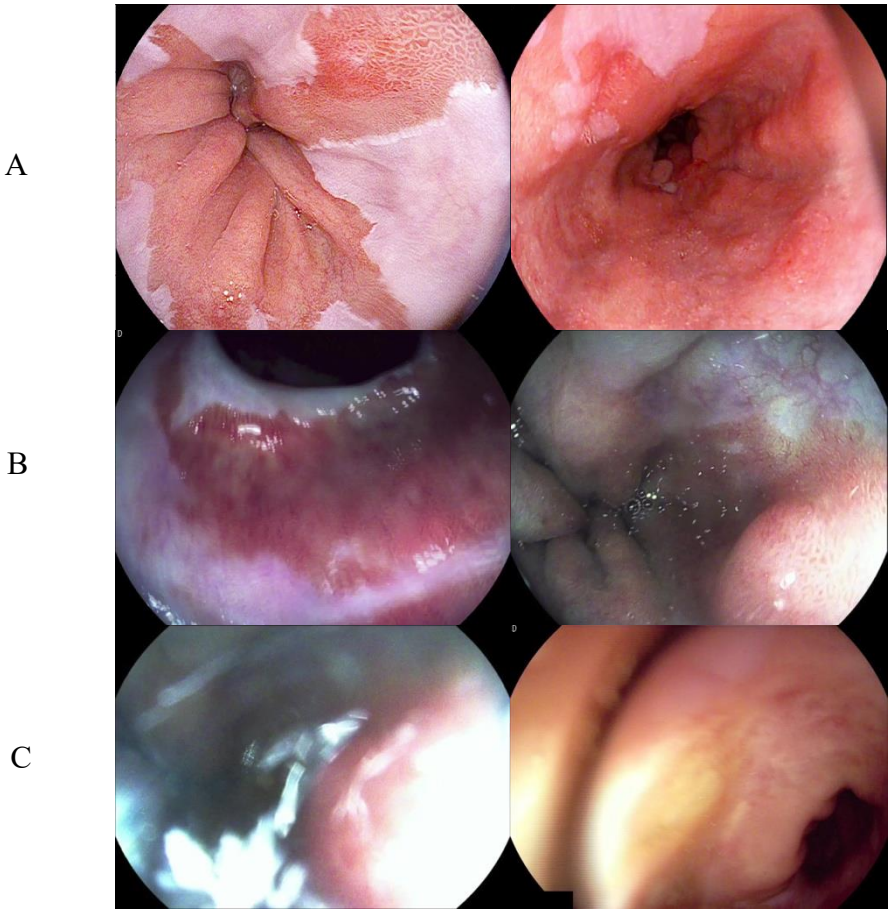


Figure 27: Using the computer vision annotation tool (developed by Odin Vision) experts delineated the area of dysplasia on a video frame. This tested the performance of the CNN in localising dysplasia and helped in the development of a second segmentation algorithm to more accurately localise the dysplastic area.

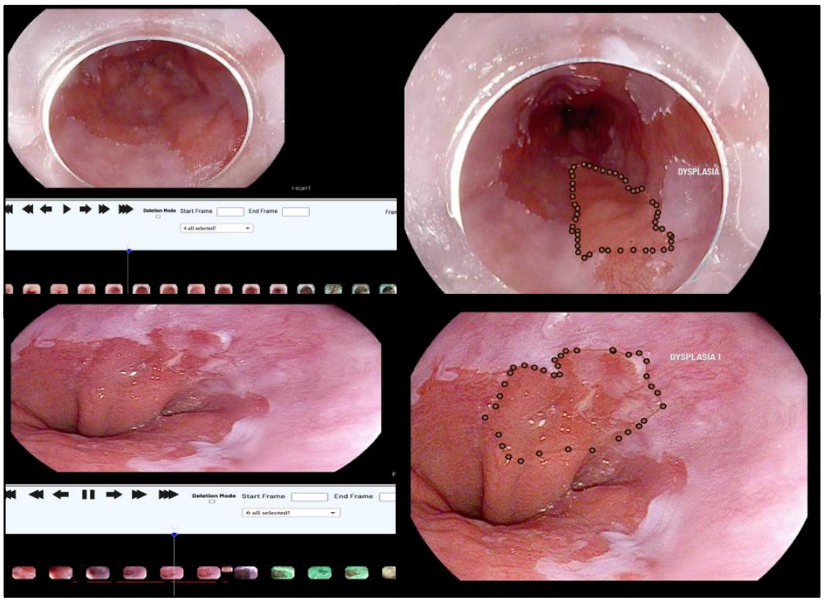
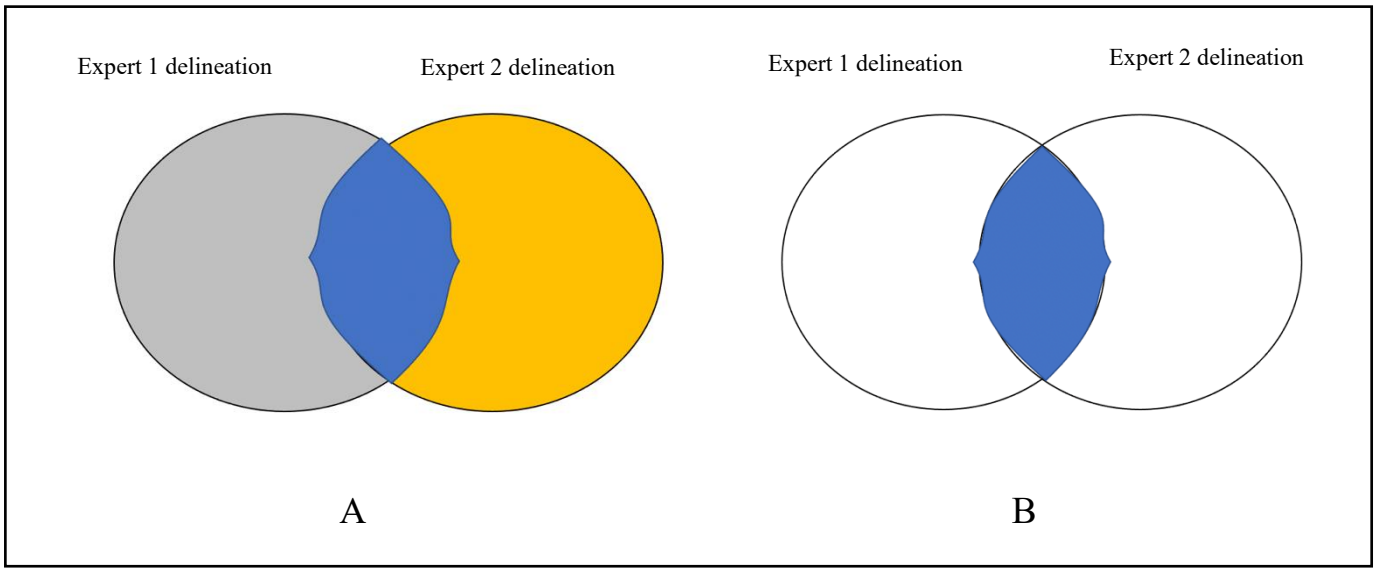


Figure 28: The performance of the CNN was tested to localise dysplasia with localisation points that (A) overlap with any of the expert's delineation areas (Shaded in grey/blue and yellow) and then tested the ability of the CNN to localise dysplasia that overlapped with the point of intersection between expert's delineation on an image (B) (area shaded in blue).



3.4.1.6 Model one: Creation of a classification convolutional neural network for the detection of dysplasia in Barrett's oesophagus

A CNN was trained with a Resnet101 architecture which can classify images as dysplastic or non-dysplastic using randomly selected frames from annotated videos. The CNN predicted a number between 0 (no dysplasia) and 1 (dysplasia present) for each pixel.

3.4.1.6.1 Data pre-processing and augmentation techniques

During training, random sampling of 5000 frames was performed on each epoch to minimise overfitting, re-sampling at every new epoch. The augmentation operations consisted of random affine transformations (rotation, translation and scale) and random colour transformations (brightness, contrast, saturation and hue) to avoid overfitting. Finally, the images were pre-processed by cropping out the video borders, followed by resizing the images to 512 by 512 pixels, and an intensity normalization step using the ImageNet channel values.

3.4.1.6.2 Hyperparameters and training

The model was trained initialising the backbone weights from ImageNet. It was trained for a maximum of 100 epochs, selecting the model with the highest accuracy in the validation set. For training, a balanced dataset was created with equal numbers of dysplastic and non-dysplastic frames from videos.

3.4.1.6.3 Training parameters:

Optimizer: Stochastic Gradient Descent, learning rate: 0.0001, batch size: 14, Image input size: 512x512px, loss: cross-entropy

3.4.1.6.4 Post-processing

The model was trained to classify over two classes: dysplastic and non-dysplastic. The output from the dysplastic class was thresholded to obtain a final prediction. The threshold was selected on each testing (different lighting modalities – iscan-1 and white light) set as to obtain a minimum sensitivity of 90%. The same threshold was used in different centres. The processing speed of the model was measured on a GeForce RTX 2080 Ti (11GB) Graphics processing unit (GPU). The methods used to generate the heatmaps was using gradient-weighted class activation mapping (Grad-CAM) (182). Grad-CAM uses the gradients of the output, for example dysplasia in BO, that are passing through the final CNN layer to generate localisation heat maps that can highlight the important areas in the output image that correspond to the areas of dysplasia in the output image that will allow a correct prediction to be made. The obtained heatmaps were generated by using the gradients corresponding to the dysplastic class.

3.4.1.6.5 The data set in the classification CNN model

This model data set included 118 different patients (the classification model in the faesability experiment in Section 3.3 included 65 patients). Cases were randomly split into training, validation and testing data sets (Figure 29). Each set was stratified to ensure consistent proportions of patients. The network was trained using 148,936 video frames. Areas of dysplasia on each frame were not delineated. A heatmap output was generated by the CNN with each prediction which showed the likelihood of dysplasia in each image.

The testing set included 44 patients (16 non dysplastic Barrett's oesophagus patients, 28 patients with dysplastic Barrett's oesophagus). Six i-scan 1 and six WL images were randomly selected per patient to generate a testing test. Two expert delineations per image on 86 dysplastic images from 28 patients helped test the reliability of the computer-generated heat map outputs in localising the area of dysplasia.

Table 9 shows a breakdown of the classifier test set based on location, Paris classification and histology.

Table 9: Breakdown of the classifier testing data set based on location, histology and Paris classification of any lesions

	Location			Histopathology				Paris classification of dysplastic lesions		
	UK	Belgium	Spain	IMC	HGD	LGD	NDBO	Paris 2a	Paris 2b	Paris 2c
Number of patients	36	3	5	15	11	2	16	16	9	3

IMC = Intramucosal adenocarcinoma; HGD = High grade dysplasia; LGD = Low grade dysplasia; NDBO = non dysplastic Barrett's oesophagus

3.4.1.7 Model two: Creation of a segmentation convolutional neural network model for the localisation of dysplasia in Barrett's oesophagus

A separate model was trained with a FCResnet50 architecture to classify pixels on a video frame as dysplastic/non-dysplastic. The backbone of the model was trained from an external data set (GRAIDS)(183). The output was a segmentation map where pixel values ranged between 0 (no dysplasia) and 1 (dysplasia present). The gold standard was two expert delineations per still image which matched with areas of histologically confirmed dysplasia.

3.4.1.7.1 Data pre-processing and augmentation techniques

During training, the augmentation operations consisted of random affine transformations (rotation, translation and scale) and random colour transformations (brightness, contrast and saturation). Finally, the images were pre-processed by cropping out the video borders, followed by resizing the images to 512 by 512 pixels, and an intensity normalization step using the ImageNet channel values.

3.4.1.7.2 Hyperparameters and training

During training, an additional auxiliary segmentation head received features from the third backbone building block. These feature maps had undergone fewer pooling steps and therefore were twice the size of the main backbone's feature maps. Thus, the corresponding segmentation output before the interpolation layer was double the resolution of the main segmentation output. A combination L aux + L main of the losses computed from the two segmentation heads was used as the final loss L, allowing to refine the spatial precision of the output. The model was trained initialising the backbone weights from a task to classify images from an external dataset (GRAIDS) as cancerous or non-cancerous(183). The rest of the model weights (the segmentation head) were initialised randomly. It was trained for a maximum of 1000 epochs, selecting the model with the highest pixel accuracy from the tuning set.

3.4.1.7.3 Training parameters

Optimizer: Stochastic Gradient Descent, learning rate: 0.001, batch size: 8, Image input size: 512x512px, loss: cross-entropy

3.4.1.7.4 Post-processing

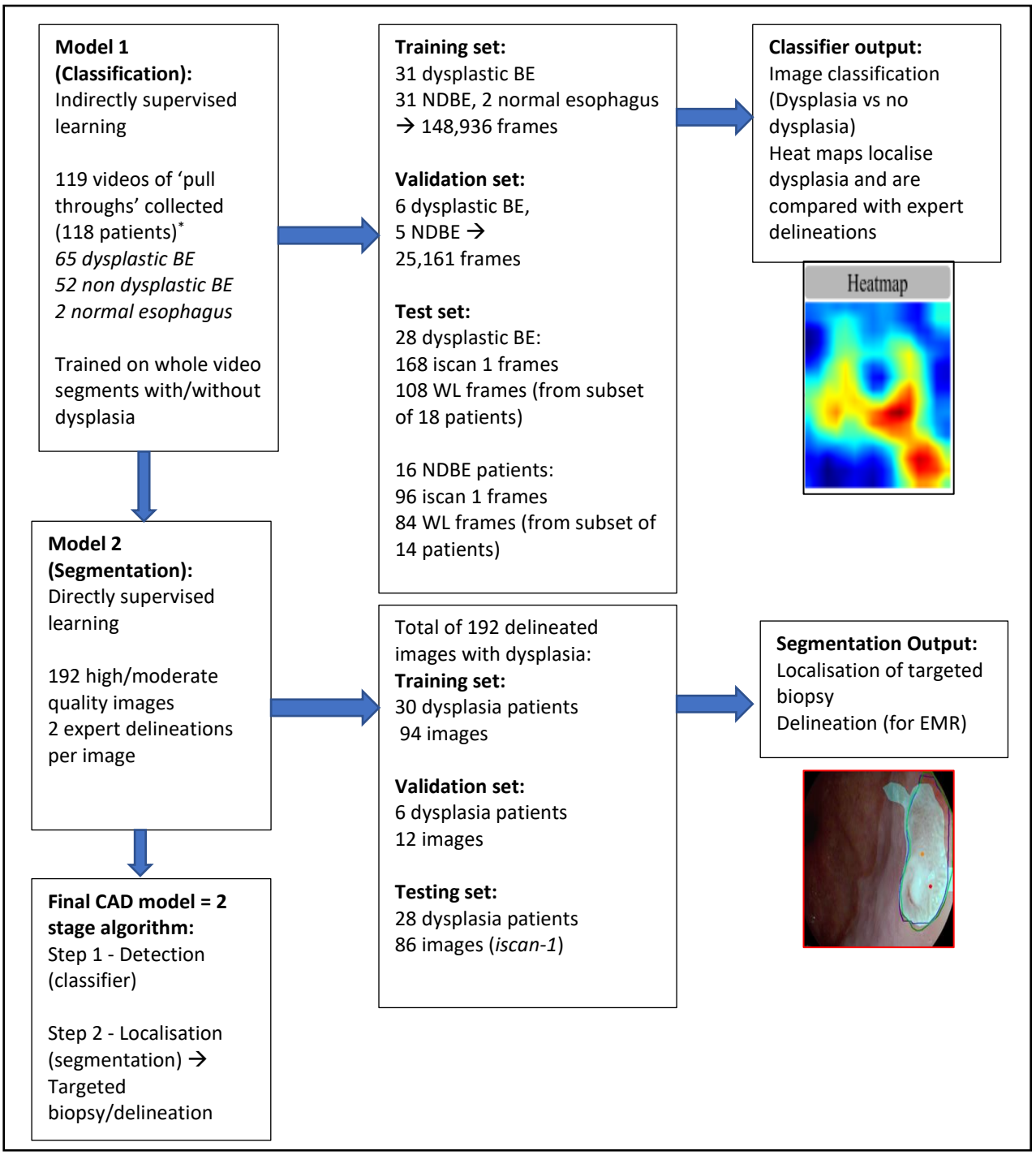
The model was trained to output a segmentation map for each input frame where pixel values ranged between 0 (no dysplasia) and 1 (dysplasia present). The processing speed of the model was measured on a GeForce RTX 2080 Ti (11GB) GPU.

3.4.1.7.5 The data set for model two

192 images containing BO dysplasia from 64 different patients were each delineated by two experts for dysplastic areas. These images were randomly selected. Further model details are in Figure 29. The patients in the independent training, validation and testing set for this model were allocated to the same three groups in the classification model to minimise bias with no overlap of data or patients. For each image of BO dysplasia, the model generated a prediction for delineation of the area of dysplasia and targeted biopsies to give a positive finding for dysplasia. One expert's delineation was used to train the network. In the testing set we included the delineation of all three experts (two delineations per frame). The performance of the network

was tested against the union of delineation of all experts on each image and against the area of overlap between expert delineations (Figure 28).

Figure 29: The overall break down of the data set in the classification and segmentation models. Description of the potential importance of each model output.



CAD = computer aided detection; **In one patient, the video segment of oesophagus was split into two segments: dysplastic and non-dysplastic BE. The former was used for training and the latter for testing*

3.4.1.8 *Comparing the performance of the AI system versus non expert endoscopists*

A subset of 61 i-scan 1 images were randomly selected from the testing set (28 dysplastic images, 33 NDBO images). Six non expert endoscopists were recruited from three centres with more than three years of endoscopic experience. A non-expert was defined as an endoscopist that does not regularly perform Barrett's assessments in endoscopy and does not perform endoscopic therapy for Barrett's oesophagus.

Each endoscopist was asked to assess for the presence or absence of dysplasia on each image on the computer vision annotation tool (Odin Vision, London, UK). Each of the endoscopists were given the same set of instructions to standardise the procedure (Appendix 1).

The performance of the classifier model in detecting dysplasia on these images was compared against these endoscopists.

3.4.1.9 *Statistical analysis*

Descriptive statistics consisted of the mean (+/- standard deviation). The sensitivity and specificity were measured at a per-image and per patient level. The area under the receiver operator curve (AUC) was also calculated.

The presence of dysplasia on a patient level was predicted using a minority and majority voting approach. These are defined below:

Minority voting approach = overall patient prediction is positive for dysplasia if this is correctly predicted in at least two out of six images per patient.

Majority voting approach = overall prediction is positive for dysplasia if this is correctly predicted in at least four out of six images from the same patient.

The Sorensen – dice coefficient was calculated and used to determine the degree of overlap between heatmaps generated from the classifier model and the expert delineations. The Dice score is a method of computing overlap between AI systems and human delineations. It is computed as:

$$Dice = (2*TP)/ (2*TP+FP+FN)$$

where true positive (TP), false positive (FP), and false negative (FN) are the total number of true positive, false positive and false negative pixels in an image respectively. A true positive pixel is a pixel where both the expert and the AI detected dysplasia, a false positive is where only the AI detected dysplasia, and a false negative is where only the expert detected dysplasia.

3.4.2 Results

3.4.2.1 Model 1 – classifier CNN for the detection of dysplasia in Barrett's oesophagus

The CNN detected dysplasia on i-scan images with a sensitivity of 91%, specificity of 79% and AUC of 93%. The AUC performance on i-scan 1 was 10% greater than on HD-WL imaging (table 10, Figure 30).

Heat maps generated from the classifier once thresholded, overlapped with at least one expert delineation in 98% of i-scan 1 images in the test set. A true diagnosis of dysplasia was made based on a minimum of 1 pixel of overlap (Figure 31). Based on a dice coefficient overlap that is greater than 20%, 78% of the heat maps overlapped with the union of expert delineations. The higher the Dice threshold, the lower the percentage overlap between the heat mat outputs and the expert delineations. Table 11 summarises the results at different dice thresholds looking at the overlap of the heat map outputs from the classifier AI system with expert one's delineation, expert two's delineation, the union of delineation of expert 1 and 2 on an image and the intersection of the delineation between expert 1 and 2. This model is trained based on thousands of frames containing dysplasia without any specific delineations of an area of dysplasia. Localisation heat map outputs are generated using an indirectly supervised approach.

Table 10: Performance metrics of the classifier model on iscan-1 and unenhanced WL imaging in the test data set

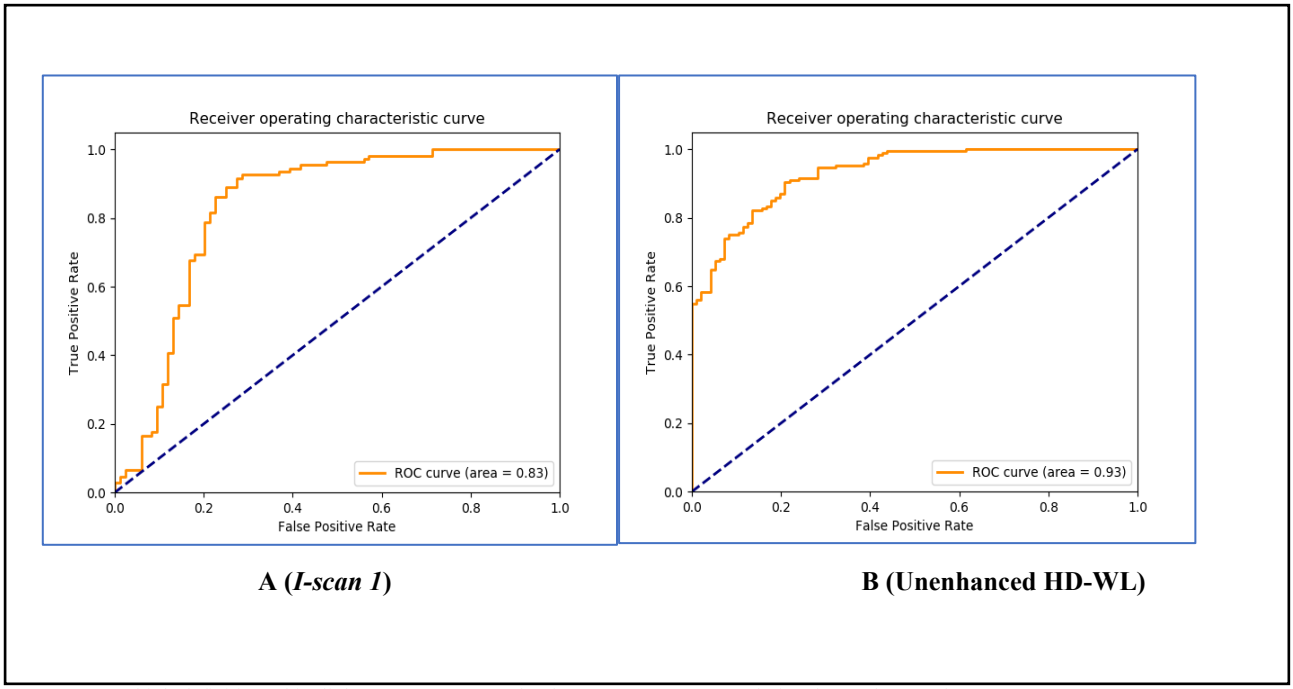
Tested on	AUC	Sens	Spec	Accuracy	Number of dysplastic patients	Number of NDBO patients	No. of dysplastic images	No. of NDBO images
I-scan 1	93%	91%	79%	86%	28	16	168	96
Unenhanced WL	83%	92%	73%	83%	18	14	108	84

AUC**;** area under the receiver operator curve, WL; White light, Sens; Sensitivity, Spec; Specificity, NDBO; Non dysplastic Barrett's oesophagus

Table 11: Based on the dice coefficient overlap a summary of the degree of overlap between classifier model heat map outputs and expert delineations at different dice coefficient thresholds. This model is not trained based on specific expert delineations. It is trained based on thousands of frames containing dysplasia within each image. Using an indirectly supervised approach the model makes a prediction using heat maps of the location of dysplasia.

Dice threshold	Expert 1 delineation with classifier heat map prediction	Expert 2 delineation with classifier heatmap prediction	Union of expert 1 + expert 2 delineation with classifier heat map prediction	Intersection of expert 1 + expert 2 delineation with classifier heat map prediction
0	98%	98%	98%	98%
10%	85%	82%	85%	82%
20%	76%	65%	78%	59%
30%	52%	44%	65%	27%

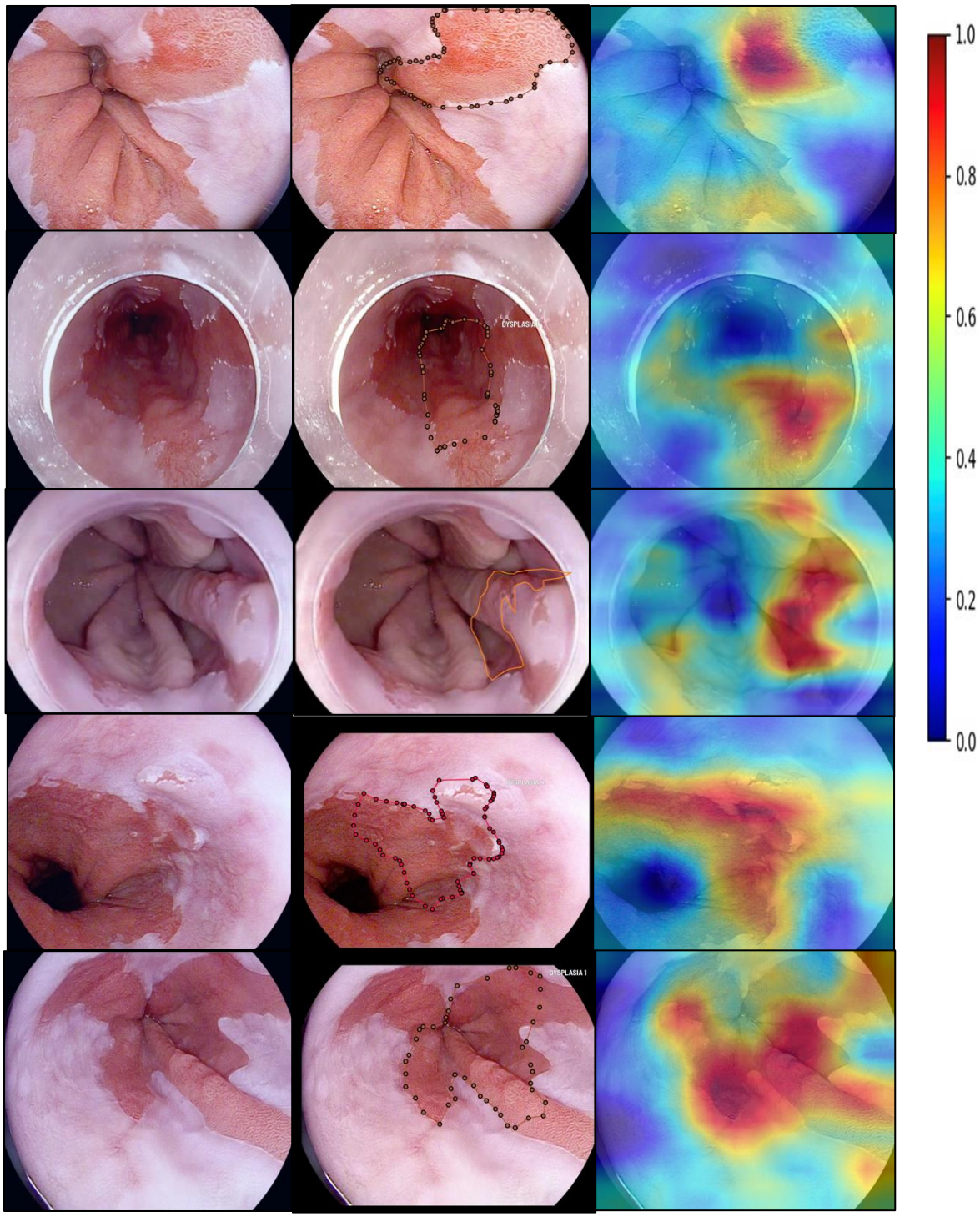
Figure 30: AUC curves demonstrating the performance of the CNN in detecting dysplasia on a)i-scan images and b) unenhanced HD-WL images.



A (*I-scan 1*) **B (Unenhanced HD-WL)**

HD-WL = high-definition white light ; AUC = Area under the curve; CNN = convolutional neural network

Figure 31: Classifier CNN heat map output. This model is trained based on video frame segments without specific delineations using an indirectly supervised approach. (A)original image, (B)expert delineation and (C) heat map output generated by the classifier. Red areas (closer to 1) show areas of likely dysplasia and therefore the sites where to potentially target biopsies or resections.



3.4.2.1.1 False negative and positive classification results on i-scan 1 images

Sixteen out of 168 dysplastic *i-scan 1* images in the testing set had a false negative classification, and 11/16 of these images were from 3 patients. 20 out of 96 NDBE *i-scan 1* images showed a false positive classification, and 18/20 of the false positives were from 4 patients (Figure 32).

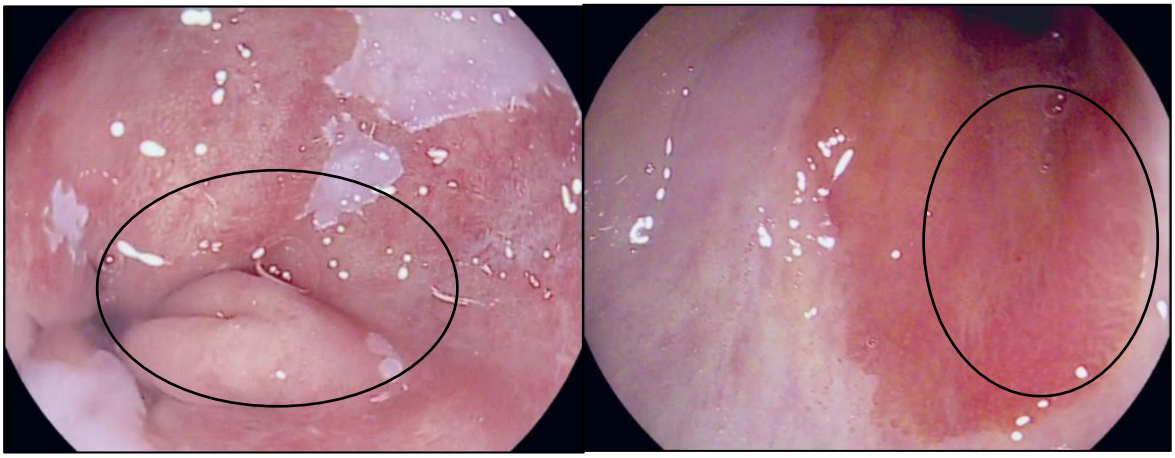
3.4.2.1.2 Classification based on histology on i-scan 1 images

In the test data set 15 patients had OAC, 11 had HGD, 2 patients had LGD and 16 patients had no dysplasia on histology. The CNN achieved a per image sensitivity of 91% which was almost identical in all the subgroups (90% OAC; 91% HGD; 92% LGD) and a per image specificity of 79% in the 16 patients with no dysplasia.

3.4.2.1.3 Per patient classification results

Using a minority voting approach on *i-scan 1* images, where at least 2 of the 6 images presented for each patient were correctly diagnosed as dysplastic, the CNN achieved a per patient sensitivity of 100%. Using a majority voting approach where at least 4 of 6 images were correctly diagnosed, the sensitivity for dysplasia detection was 89.3%.

Figure 32: Example of a false positive classification prediction (A) due to a prominent gastric fold at the gastroesophageal junction. (B) a false negative prediction in an area of subtle, flat high-grade dysplasia



A **B**

3.4.2.2 Model 2 – Segmentation CNN model for the localisation of dysplasia in Barrett's oesophagus

Two different scenarios were generated for the localisation of dysplasia in Barrett's oesophagus:

1- Targeted biopsy – localisation of points of interest in BO suggestive of dysplasia
2- Localisation with an area of delineation of dysplasia in BO

Both scenarios predicted areas of interest in BO which are suggestive of dysplasia which can either be target biopsied or in an expert BO centre resected with an EMR.

3.4.2.2.1 Localisation of points of interest of dysplasia in Barrett's oesophagus with a targeted biopsy

Different scenarios were generated for targeted biopsy predictions using:

- The maximum positive pixel value in the raw predicted segmentation output
- Geometric centre of the segmentation delineation. This can be one or multiple points depending on the predicted scenario or segmentation.

A targeted biopsy was considered correct if it fell within the area predicted by expert endoscopist delineations which matched with biopsy histology and/or EMR's.

Six different scenarios for targeted biopsy predictions were generated which are summarised in table 12. The meaning of each scenario was as follows based on geometric centres and pixel values:

Scenario one = 1 point of interest – one geometric centre = 1 targeted biopsy

Scenario two = 1 point of interest – one maximum pixel values = 1 target biopsy

Scenario three = 2 points of interest – one maximum pixel value and one geometric centre = 2 targeted biopsies

Scenario four = 3 points of interest – one maximum pixel value and two geometric centres (could be less geometric centres depending on how many segmentation delineations in the prediction) = 3 targeted biopsies

Scenario five = varying numbers of point of interests but all geometric centres

Scenario six = all points of interest - one maximum pixel value and all geometric centres.

Scenario three balances the number of targeted biopsies with high performance and was the optimal scenario to incorporate into an endoscopic system in real time. Based on this scenario the AI model recommended targeted biopsies within the intersection of expert delineations with a sensitivity of 78%, and within the union of expert delineations with a sensitivity of 91% in the model 2 test set of 28 patients with dysplasia. When allowing for the system to generate any number of targeted biopsy predictions the sensitivity for localising dysplasia was 86% in the intersection of delineations and 97% in the union of delineations. (table 12)

Table 12: Targeted biopsy predictions by the CNN model for areas of dysplasia in BO. Outcomes based on the overlap of the targeted biopsies with expert 1, expert 2, union of the delineation of both experts and the intersection of the delineations of the experts are summarised below. Each scenario was formulated based on the maximum positive pixel value in segmentation heatmaps and geometric centres of the segmentation delineations. Based on expert consensus the optimal scenario was number 3.

	Mean number of biopsy predictions	Maximum number of biopsy predictions	Targeted biopsy within expert delineation 1	Targeted biopsy within expert delineation 2	Targeted biopsy within intersection of expert delineation 1 and 2	Targeted biopsy within union of delineations of expert 1 and 2
Scenario 1	1	1	72%	62%	57%	77%
Scenario 2	1	1	81%	74%	71%	85%
Scenario 3	2	2	88%	81%	78%	91%
Scenario 4	3	3	91%	85%	81%	93%
Scenario 5	2	4	86%	84%	78%	91%
Scenario 6	3	5	94%	90%	86%	97%

3.4.2.2.2 Localisation of dysplasia in Barrett's oesophagus with delineation

Segmentation delineations generated by the segmentation CNN predicts an area which potentially contains dysplasia. A prediction was made on all 28 dysplastic cases in the model 2 data set. The segmentation model delineations overlapped with at least one expert delineation in 98% of images with a minimum of one pixel of overlap. The segmentation delineation had a 50% average dice score with expert one.

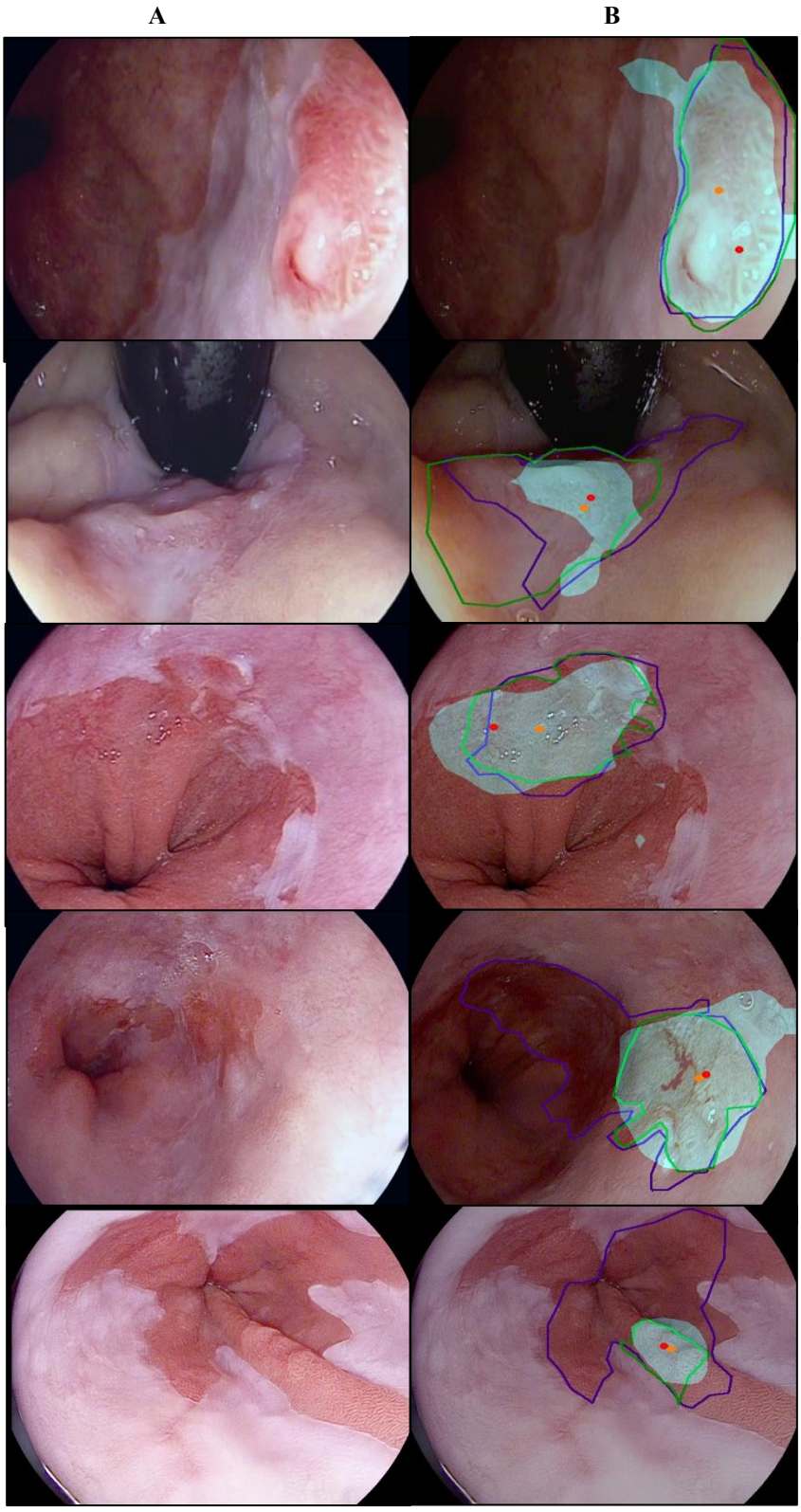
Figure 33 gives examples of the discussed scenarios in this section. Each image contains two expert delineations which outlines where the endoscopists thinks there is dysplasia in BO (blue

and green outline), the thresholded (0.5) heatmap segmentation output from the model (light blue shaded area) and red (maximum positive pixel value) and orange (geometric centre) point of interest dots.

3.4.2.3 Detection speed of dysplasia in Barrett's oesophagus

The mean (+/- standard deviation) time for the analysis of each image by the classifier CNN was 0.021 seconds per image (+/- 0.008), or 47 frames per second (fps). The mean time for the analysis and delineation of dysplasia on each image by the segmentation network was 0.018 seconds (+/- 0.006) or 55 fps.

Figure 33: BO dysplasia (A) and the targeted biopsy and segmentation delineation CNN predications (B) relative to expert delineations. Delineations (green and purple outline) are the two different expert delineations per images. Blue shaded delineations = segmentation delineation by CNN. Red and orange dot = targeted biopsy prediction by CNN.



3.4.2.4 Comparison of the performance of the AI system versus non expert endoscopists

All six non expert endoscopists detected dysplasia in BO on i-scan 1 images with a mean sensitivity of 79% and specificity of 49%. On the same subset of testing set images the Classifier CNN was able to detect dysplasia with a sensitivity of 96% and specificity of 88%.

Table 13 summarises the break down performance of all 6 non expert endoscopists versus the AI system.

Table 13: The breakdown performance of the six non expert endoscopists in detecting dysplasia in BO in comparison to the AI system

	Per image sensitivity	Per image specificity	Mean
Endoscopist 1	23/28 (82%)	19/33 (59%)	Sensitivity = 79%
Endoscopist 2	21/28 (75%)	12/33 (36%)	Specificity = 49%
Endoscopist 3	16/28 (57%)	22/33 (67%)	
Endoscopist 4	24/28 (86%)	22/33 (67%)	
Endoscopist 5	22/28 (79%)	15/33 (46%)	
Endoscopist 6	26/28 (93%)	7/33 (21%)	
AI system	27/28 (96%)	29/33 (88%)	

3.4.3 Discussion

This experiment demonstrates for the first time a computer aided detection system which can accurately detect and localise early cancer in BO using the Pentax endoscopic imaging system. There is a high per image sensitivity and specificity of 91% and 79%, respectively on i-scan 1 imaging.

We demonstrate two methods for localisation. One using an indirectly supervised approach using heat maps generated from the classifier CNN. These overlapped with at least one expert endoscopist delineation with a minimum of one pixel overlap in 98% of the images. The classifier

models are not trained with segmentation delineation images however with a dice threshold of 10%, the heat maps generated from the classifier CNN had an 85% overlap with the union of expert delineations, and 82% overlap with the intersection of expert delineation. This indicates that the models are basing their predictions on the correct areas in terms of dysplastic features without being specifically trained to do so. This might be due to the large volume of frames of data the classifier model is trained on (148, 936 frames) and wide variety of data in the training data set (31 dysplastic BO, 31 NDBO, 2 normal oesophagus). This approach may be useful as it works fast, can potentially identify areas of interest in BO with heat map overlays and does not specifically need experts to delineate every frame as has been done in previous studies (124)(122)(121). Expert delineations can be time consuming and potentially a limiting factor in developing some of these models for BO dysplasia detection as a smaller volume of images can be realistically delineated by humans due to the pressures of time. Further studies with a larger data set are required to validate this methodology. We chose to use an indirect learning approach to generate heat map outputs from the classifier and assess whether they help endoscopists to identify areas of interest in BO without the need for expert delineations for training, to provide insight into how the classifier makes its prediction per image, and to compare against the output of the segmentation model for delineation (directly supervised approach) as a pilot to see if this methodology could have potential implications on the way we train and process data when developing BO CAD systems.

We also developed a second directly supervised CNN segmentation model trained on delineations generated by experts which are matched with EMR/biopsy histology This was able to localise areas of interest with a sensitivity of up to 97% with targeted points of interest. The number of points of interest generated can be tailored. The optimal scenario was scenario three which balances the maximum number of biopsies (two) with a high performance. (Table 12, Figure 33). Delineation predictions were also generated from the segmentation model which had an overlap of 98% with the union of expert delineations (50% average dice score with expert one). Realistically the targeted biopsy would be most clinically relevant in all non-expert centres. These centres would want to localise the area of interest with a biopsy and make sure these early cancers are not missed. The clinical workflow would be if the histology is positive for dysplasia or early cancer the cases can then be referred on to an expert centre for an EMR or ESD. Therefore, this would be what is most clinically relevant globally to use as the segmentation model output and during real time endoscopy. During all these experiments the real-world

workflow was kept in mind to make these models as relevant as possible to common clinical scenarios in endoscopy.

Both the classification model and segmentation model can form part of a two-step computer aided detection system algorithm which can be translated into a working endoscopy unit in real time. The system would generate a prediction on still frames as the endoscopist is performing a pull through withdrawal in the oesophagus. If the classifier is positive for dysplasia, then using the segmentation CNN a targeted biopsy point is generated on the image for where to take a tissue sample. Freeze image captures are required as part of standard of care during an assessment of BO. These CNNs understandably would perform better on higher quality still frames. It therefore was felt it would make more sense to generate a prediction on the still images. In a similar fashion if an endoscopist has concerns about an area they would normally take an image as part of standard of care. A prediction can be generated on this still image. The oesophagus is associated with a lot of spasms and potentially fluid refluxed from the stomach and therefore it would be important to maximise the cleanliness of the images and to generate an environment where it would be easiest for the AI system to make the most accurate prediction. Figure 34 shows a potential workflow of how this AI system would work in endoscopy.

We have shown in Section 3.3 in the feasibility experiment the performance of a classifier CNN model on thousands of frames. On almost 190,000 frames in 19 different cases the CNN was able to classify dysplasia with a sensitivity of 88% and specificity of 80%. High quality images were not selected in that experiment and the performance of the classifier model was evaluated on all available frames. To evaluate a direct comparison of performance of models on high quality still images versus all available frames this would require the same training/validation and test set split in both experiments. What can be concluded from this indirect comparison is that performance on high quality frames is likely to be better based on the sensitivities achieved on a larger testing data set. A direct comparative study would be required to accurately evaluate this hypothesis.

Von ebigbo et al demonstrated a CNN trained on still images from two different databases which achieved a sensitivity/ specificity of 97%/88% and 92%/100% on white light for the two different datasets from two separate centres. The histology of the lesions were early oesophageal adenocarcinoma (128). De Groof et al developed a promising hybrid ResNet-UNet model computer aided detection system using five independent endoscopy data sets. They pre-trained

using 494,354 labelled endoscopic images from the GI tract. The data set was then trained using high quality delineated BO images. In the final data set they compared the performance of the AI system against 53 non expert endoscopists. The CAD system had a higher performance compared to endoscopists based on all metrics (88% versus 73% accuracy, 93% versus 72% sensitivity and 83% versus 74% specificity). The optimal biopsy site was identified in 97% and 92% of cases in the two final datasets (123). In the current study a different approach to previous studies in how we trained the classifier model. Training was done using a large number of BO frames (dysplastic and non-dysplastic, 148,936 frames) from a large number of individual patients (N =64) each with a video assessment. Multiple frames per video were used to train the CNN rather than select few high-quality images per case to provide valuable information for the CNN's, maximise the training data set and most importantly to maximise the ability of the network to work in different environments in real time.

A difference in this study in this chapter is that LGD was also included in the testing set. Previous studies did not include LGD. The CNN achieved high sensitivities in detecting OAC, HGD and LGD. I felt it was important to include this subgroup within the testing set as these lesions can be upstaged following an EMR. Tsoi et al showed that a tertiary referral centre for BO identified more visible lesions in BO compared to non-expert centres. 27% of patients referred from non-expert centres were diagnosed with HGD or OAC following a recent diagnosis of LGD in non-expert centres (184). Also as discussed in the experiment in chapter 2 where I assessed the natural history of LGD in BO, 33% of patients with true confirmed LGD and had never had ablation treatment had progressed to HGD/OAC. This shows the importance of also detecting LGD in BO and offering early curative endoscopic therapy.

Previous studies of AI in BO had trained and tested networks using the Fujinon and Olympus endoscopic systems (123) (122) . This is the first study to my knowledge where a CNN for dysplasia detection in BO was developed using the Pentax endoscopic imaging system. On this imaging system i-scan 1 is often the default initial modality instead of white light. It provides the same natural colour tone of white light but has the added advantage of surface enhancement therefore improving the chances of dysplasia detection. As a result of this the testing set was composed of a larger volume of i-scan 1 frames compared to white light. The results suggest a better performance of the CNN on i-scan 1 compared to white light which is what you would similarly expect in Human endoscopists. Bowman et al showed that on i-scan 1 significantly more colonic adenomas were detected compared to on high definition white light imaging (185).

With Seattle protocol biopsies performed during BO surveillance endoscopy this would sample only a 3.5% of the whole BO segment (116). If dysplasia is focal this can potentially be missed despite Seattle protocol biopsies being adhered to. There are also other disadvantages associated with this sampling technique including sampling error, bleeding risks, poor adherence by endoscopists and prolonged procedures if the BO segment length is long which can have an impact on a patient's tolerance of a procedure (112). A CNN was developed using a segmentation algorithm which can localise areas of dysplasia with targeted points of interest on the image. It can perform this with an accuracy of up to 97% if allowing for any number of biopsy points. Various scenarios were generated using the maximum positive pixel value in the raw predicted segmentation output and geometric centre of the segmentation delineation (Table 12). Based on expert consensus the optimal scenario was number three which balances a high performance and limited number of biopsies (Accuracy of 91% of correctly detecting the area of dysplasia which overlaps with the union of expert delineation. There is a maximum of two targeted biopsy predictions in this scenario). These performances were generated on i-scan 1 imaging because as discussed previously this would be the imaging modality of initial choice on Pentax imaging for detection and therefore it would make sense to generate the targeted biopsy predictions on this imaging particularly as initial pull through assessments of the oesophagus will be performed normally on this light modality.

With the targeted biopsy predictions, the clinical workflow would be that in biopsy positive patients with dysplasia they would then be referred on to the expert BO centre for curative endoscopic therapy. This could be with an EMR or ablation treatment of BO if there are no visible lesions. These computer aided detection systems for BO would be more useful in non-expert centres with a lower volume of BO referrals to minimise miss rates of early cancers or early dysplastic lesions that can potentially progress in future if not treated early.

Six images per cases in the testing set were selected to test the performance of the classifier CNN in Section 3.4. This reflects the clinical workflow where during a pull through assessment of the oesophagus endoscopists would take relevant freeze frame images which would normally be done as standard of care. The freeze frame images would normally be of a higher quality with minimal artefact. Therefore, the AI system would have the highest chance of an accurate prediction. A pilot study tested the performance of an AI system during live endoscopic assessment of BO on still images. They used a minority as well as a majority voting approach in

order to categorise an area of BO as dysplastic versus non dysplastic (124). There was a per patient sensitivity of 90%. In the current study I use a minority and majority voting approach to categorise dysplasia on a per case basis. At least 2/6 and 4/6 correctly classified images were necessary on each case using the minority and majority voting approach respectively. A per patient sensitivity of 100% and 89.3% were achieved respectively on i-scan 1 images.

Different studies have developed computer aided detection systems for dysplasia in BO which have varying speeds. Normally to be able to fairly compare the speeds of different systems they would need to be benchmarked on the same machine. Studies by De Groof et al developed CNN's which were able to detect dysplasia with an average speed of 1.051 and 0.191 seconds per image (123)(122). The CNN in this chapter was able to detect dysplasia using the classification CNN with an average speed of 0.021 seconds per image. This shows that the AI system is potentially able to support the decision making of endoscopists in real time.

Since the publication of the work in this chapter Fockens et al developed a computer aided detection system which was tested in 3 different test sets. It had sensitivity performances ranging from 84% to 100%. Specificity ranged from 64% to 66%. The System outperformed a large group of endoscopists in terms of sensitivity, but not in terms of the specificity (186). More recently the same group developed a deep learning system which improved the sensitivity of neoplasia detection in BO from 74% to 88% without having any compromise on the specificity. The data set in both of these studies consisted of frames from Olympus endoscopic system(187).

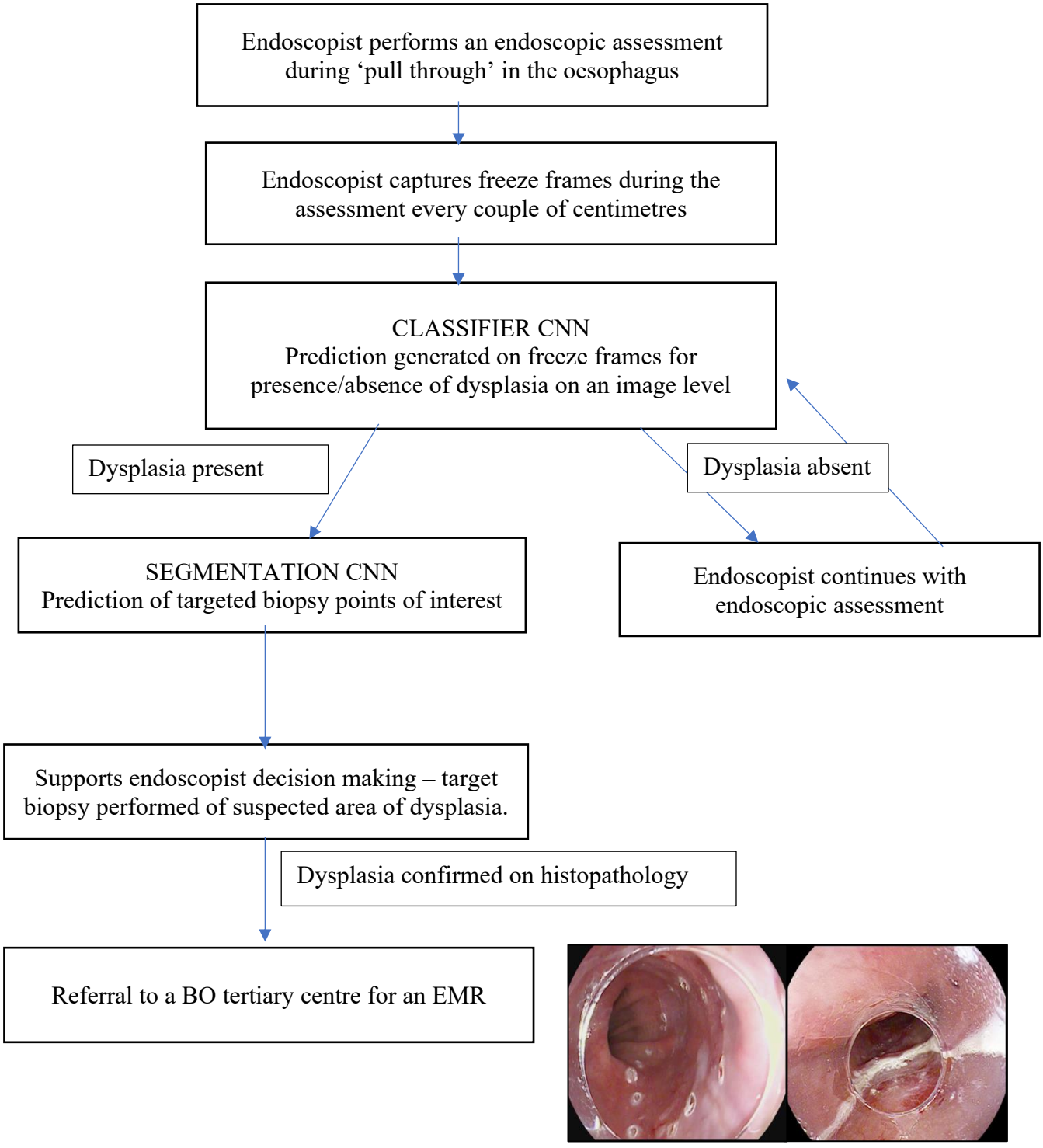
The performance of the AI system was measured against six non expert endoscopists. The experience of these endoscopists in upper GI endoscopy ranged from 3 to 11 years. This is the group of endoscopists I felt an AI detection system for dysplasia would be of most benefit potentially and where the miss rate of early cancer can be minimised. For this experiment a small subset of testing set images were selected. This is to ensure that all endoscopists would complete the task. The AI system performed better than each individual endoscopist in terms of sensitivity and specificity for detecting dysplasia. The average specificity of endoscopists was 49% suggesting that there was a significant over prediction for the presence of dysplasia. This is likely due to the lack of experience in assessing BO. Therefore, they would be more likely to take more biopsies due the lack of clarity of what is normal versus abnormal in BO. The results were compatible with outcomes in other studies comparing the performance of the AI system which outperforms non expert endoscopists. De groof et al compared the performance of the

CAD system to 53 non- expert endoscopists. A higher accuracy was achieved with comparable delineation performance(123). This data consisted of Olympus and Fujinon endoscopes (FUJIFILM, Tokyo, Japan). I used Pentax endoscopes in this study.

Figure 34 demonstrates the potential clinical workflow of the two staged algorithms (classification for detection followed by segmentation for localisation of early cancer) in the endoscopy unit.

The results of the BOSS study (discussed in section 1.1.9.3) showed that Barrett's surveillance did not improve cancer specific and overall survival (85). Therefore there will likely be a bigger push for higher quality endoscopy in the coming year before patients are discharged from surveillance programmes. A Barrett's AI system could potentially support this by confirming a negative endoscopy and agreeing with an endoscopic and histological assessment. What will be needed in future work is developing a robust AI quality system to ensure the endoscopic assessment oesophagus is of a high enough quality. This would serve the purpose of improve dysplasia detection rate but also maximising the chance of an accurate prediction by the AI system.

Figure 34: The clinical workflow of how the computer aided detection system would fit into the decision-making process in the endoscopy unit



3.4.4 Study limitations and future work

There were some limitations in the study which one could improve on in future work. This included:

- A CNN was developed using a single endoscopic system. For it to be generalised across all endoscopic platforms it would need to be trained using other endoscopic systems using a balanced training set inclusive of imaging from all the other main endoscopic imaging systems. This would allow for a more generalisable CNN. In future studies it would be ideal to include data from different endoscopic systems. I wanted to trial this by developing this on a single endoscopic system in the first instance (Pentax) and make this robust.
- The CNN for detection of dysplasia is tested on high quality images in the testing set. If tested on all available data during a pull through the outcomes are likely to be worse. In the future work I would aim to see how the CNN performs during a pull through of the oesophagus where temporal filtering can be used to make a prediction over several frames in the oesophagus. This would allow the CNN to make an overall prediction of the presence/absence of dysplasia in the oesophagus.
- The test in the model 2 segmentation experiment in section 3.4 was 86 images. It would have been more ideal to have a larger test set however in this experiment all the images required delineation by two expert endoscopists per image. Realistically one must balance the size of the data set with the amount of available time expert endoscopists have to delineate the data. In future this could be rectified by selecting a larger number of expert endoscopists to minimise each of the endoscopists workload and create a larger testing set.
- The segmentation model was trained based on the delineation of one expert endoscopist. To create a more accurate model in future work it would be best to train the segmentation model based on the intersection of expert delineations. This would potentially improve the localisation ability of the computer aided detection system.
- The data set for i-scan 1 was larger than the white light data set in the classification experiment in section 3.4. This would need to be considered when assessing the improved performance of the CNN on i-scan 1 versus white light. In future studies it would be best to perform matched studies to more fairly compare performance of dysplasia detection on the two imaging modalities. I would match the number of images used, histology and Paris classification of lesions.

3.5 Summary of the chapter

In this chapter assessing the performance of an AI system in the detection and localisation of dysplasia in BO I demonstrate:

1. A computer aided detection system which can detect dysplasia on a per image and patient level on both white light and i-scan 1 imaging with a high sensitivity and specificity.

2. That heat maps can be generated from the classifier CNN that can potentially localise an area of interest with dysplasia with an unsupervised learning approach. There is a 98% overlap between the heat maps and expert delineations based on a minimum of 1 pixel of overlap.

3. A computer aided detection system which can localise dysplasia with targeted biopsies with an accuracy of up to 97%. This would be particularly useful in non-expert BO centres to improve the pick-up rate of dysplasia. If HGD or intramucosal cancer is detected this can then be referred to an expert centre for curative endoscopic therapy with an EMR or ESD.

4. We compare the different approaches to the development of a CNN for localisation of dysplasia in BO using a supervised (Segmentation algorithm) and unsupervised (Classifier algorithm) learning approach. The unsupervised learning approach will still require more validation with larger scale experiments, but the findings are promising as there is not a need for expert delineations which can be time consuming for experts.

5. There is a superior performance of the AI system versus non expert endoscopists in detecting dysplasia in BO. This experiment demonstrates that non experts are where these AI systems may play a major role in future to maximise detection. These AI systems may also play a role as part of the training programme in helping improve training of new endoscopists.

6. To the best of my knowledge this is the first published Artificial intelligence system for the detection of dysplasia in BO developed using Pentax imaging.

CHAPTER 4

THE DEVELOPMENT OF DEEP NEURAL NETWORKS FOR THE CHARACTERISATION OF DYSPLASIA IN BARRETT'S OESOPHAGUS ON MAGNIFICATION IMAGING

CHAPTER 4 THE DEVELOPMENT OF DEEP NEURAL NETWORKS FOR THE CHARACTERISATION OF DYSPLASIA IN BARRETT'S OESOPHAGUS ON MAGNIFICATION IMAGING

The work presented in this chapter formed the basis of a peer reviewed publication. Text and some of the figures were adapted for publication. Citation(188):

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4.1 Introduction

As discussed in chapters 1, 2 and 3 BO is associated with an increased risk of progression from NDBO to LGD, HGD and then oesophageal adenocarcinoma (119). Despite all the advances in endoscopic technology studies have shown that there is an oesophageal cancer miss rate of 6.4% during routine endoscopy (189).

The assessment of BO during a pull through assessment of the oesophagus can be looked at as part of a two-step process. The BO segment is initially carefully assessed in overview during a pull through on high-definition white light imaging modes or using the i-scan 1 modality if using the Pentax endoscopic systems. If an area of interest is identified this can then be assessed with magnification imaging. This would be done using chromoendoscopy and in the case of Pentax imaging done using the i-scan 3/ optical enhancement imaging mode. This would give a clearer visualisation of the mucosal architecture and vasculature (129). It would also be particularly useful in delineating the resection margins in an expert centre to allow a complete endoscopic resection to be achieved (R0).

Despite the presence of classification systems for characterisation of dysplasia in BO this might be difficult for non-expert endoscopists who are not used to using such imaging modalities regularly (190)(191)(192)(193)(181).

The focus of the experiment in this chapter is using i-scan 3/optical enhancement (OE) imaging. This uses pre- and post-processing techniques to allow the surface enhancement of superficial mucosal vascular structures. An optical OE filter delivers specific wavelengths of light which correspond with the main absorption spectrum of human haemoglobin. This allows for the enhancement of the vasculature structures in the superficial mucosal layers. This imaging modality combined with the magnification function allows a much closer inspection (up to x 136 resolution) of the mucosal pit pattern and vasculature (96).

Everson et al showed that the accuracy of neoplasia detection and histological prediction in BO was higher on OE magnification endoscopy versus high-definition white light. This was the case in both experts and non-experts (96). A simple classification system was used. Lipman et al used an i-scan classification system for BO in combination with magnification imaging. This detected dysplasia with a good accuracy (194).

To the best of my knowledge the only other study to develop an AI system for the characterisation of dysplasia in BO on magnification imaging at the time of publishing the work discussed in this chapter was a paper by Struyvenberg et al (129). They developed a system with promising accuracy in characterising dysplasia on narrow band imaging zoom videos using the Olympus system. The work in this chapter to the best of my knowledge was the only published work using the Pentax imaging system at the time of publication.

In this chapter the experiment for the development of a computer aided diagnosis system for the characterisation of BO on chromoendoscopy will be demonstrated. An initial methodology will be shown followed by the final experiment following adjustments made to the feasibility experiment. The idea behind all the experiments was to always keep a real-world perspective and make the outputs relevant to how an endoscopist performs a procedure such that the algorithms can be potentially as useful as possible in the real-world scenario. The main idea for this algorithm on magnification imaging was to support the detection algorithm from chapter 3 as part of a two-stage process. It would help support experts with endoscopic resection with clear resection margins and support non experts who are not clear on a diagnosis following detection of a lesion using the CNN in chapter 3. This would also potentially allow for the increased uptake in the use of magnification endoscopy in non-expert centres if this process is automated.

Theoretically you would be able to train a CNN much more easily on magnification imaging due to the clarity of the vessels and mucosal architecture to then be able to develop a classifier.

4.2 Aims of the experiment

The overall focus of the experiments in this chapter were to develop a robust AI system that can aid endoscopists with the characterisation of dysplasia and early neoplasia on magnification imaging during a BO surveillance assessment. There were two main aims to this chapter:

1- To develop a computer aided diagnosis system that can diagnose dysplasia in BO on i-scan 3/OE magnification endoscopic imaging on 3 different levels:

a. High quality still images – selected high quality frames to reflect the real-world decision-making process where endoscopists can freeze an image to make an assessment and diagnosis on magnification imaging.
b. Short sequence of frames – continuous sequence of frames reflecting the real-world decision-making process where an endoscopist will make a decision based on a short assessment of a section of the oesophagus.
c. On whole videos of the oesophagus – assess the performance of the CNN on all the available frames from the oesophagus. It may be more than one different location in the oesophagus which has been assessed. This would gauge the overall robustness of the model.

2-Secondary aims were to assess the speed of the networks in diagnosing dysplasia and early cancer in BO on magnification endoscopy.

4.3 Initial feasibility experiment for the development of a neural network to classify for the presence of dysplasia in BO on magnification endoscopy

This section will discuss the initial experiment that was performed to develop a neural network which can classify the presence or absence of dysplasia in BO on magnification imaging. At the time of performing this experiment the area of the use of AI on magnification endoscopy to assess BO was a novel area. There was only one publication on this area which was done on the Olympus endoscopic imaging system(129). The experiments in this chapter are performed on

Pentax imaging like the experiments in Chapter 3 to maintain consistency. To the best of my knowledge this has not been done before and therefore novel. This chapter will reflect the initial strategy used to develop this CNN and how this then went on to lead to my main experiment in section 4.4.

4.3.1 Methodology

4.3.1.1 Patient recruitment

Patients attending assessment for BO at four European centres were recruited. All cases were collected prospectively as part of the current and previous BO imaging study. Patients were excluded if there was oesophageal varices/ulceration or oesophageal strictures. The study was approved by the Cambridge central research ethics committee (REC Reference No. 18/EE/0148) for UK sites. European centres received ethical approval from local committees for use of images for this and other imaging-based research projects.

4.3.1.2 Endoscopic procedures and video collection

Videos were collected by four expert BO endoscopists. All endoscopists had more than 10 years' experience in BO assessment and endoscopic therapy, performed BO endoscopic therapy weekly and have zoom endoscopes and Pentax imaging systems on their units.

During the video collection procedure, the mucus lining the oesophagus was removed using a simethicone and water solution. Endoscopists performed a pull through of the oesophagus during initial endoscopic assessment. If an abnormality was identified this is assessed using the x 136 zoom endoscope using high-definition white light, i-scan 1 and i-scan3/OE imaging. If no lesion in keeping with dysplasia/early cancer was identified the endoscopist would select one normal area in BO and assess this using the same x 136 zoom endoscope using high-definition white light, i-scan 1 and i-scan3/OE imaging.

4.3.1.3 Tissue acquisition and histology

During the BO assessment areas of the oesophagus suspicious for dysplasia were either target biopsied or resected with an EMR. The EMR specimens were affixed to a cork with pins and needles and then embedded in paraffin in the histopathology laboratory. Areas without suspicion of dysplasia and looked like normal BO mucosa were target biopsied and sent for

histopathological assessment. Histology with dysplasia were reviewed by two expert BO histopathologists with more than 10 years of experience in each respective centre. The dysplastic lesions in this study were HGD and intramucosal adenocarcinoma.

4.3.1.4 Annotation

Videos were uploaded on to a computer vision annotation tool (Odin vision, London, UK). This was used to annotate the frames as 'dysplasia' or 'no dysplasia' based on the vascular and mucosal pit pattern. The area of annotation matched with the EMR or biopsy histology which was considered the gold standard. These frames were used to train a CNN.

4.3.1.5 Model data set

58 different patients were included (34 dysplasia, 24 NDBO). Performance was evaluated using a 15-fold cross validation methodology such that all the data was used for testing and training by varying the testing/training split in each independent fold. The training and testing set included high-definition white light, i-scan 1 and i-scan 3/OE magnification imaging. In total 76,496 magnification video frames (29,058 non-dysplastic, 47,438 dysplastic) composed of white light, i-scan 1 and i-scan 3/OE images were analysed by the neural network. In this experiment all imaging modalities were included and all available frames.

4.3.1.6 Convolutional neural network

4.3.1.6.1 Pre-processing and augmentation

The CNN was trained using a ResNet101 architecture using a 15 fold cross validation methodology (195). All the data was used for testing and training by varying the training and testing splits in each fold. Each fold is trained for the same number of epochs and tested on the same epoch which ensures that we are generalising across the data. An epoch is one passing of the training data through the algorithm.

Overfitting is tightly fitted with the training data and therefore does not generalise to a new testing data set. Data augmentation is a method to reduce overfitting and increasing the training data set by making subtle changes to the training data set. Data augmentation was performed randomly to reduce overfitting, including colour transformations (brightness, contrast, saturation

and hue) and affine transformations (rotation, translation and scaling). The training parameters were kept the same for each of the 15 folds and then tested across all folds to ensure there is no overfitting. Mini-batch training was done where a training iteration is performed with different mini-batches of 5000 training images.

The image region is cropped (removing the black borders), the image is resized to 448x448 pixels and then the pixel values are normalised.

4.3.1.6.2 Hyperparameters and training

The CNN was pre-trained on image-net and fine-tuned on our data. Learning rate of 1e-5, Fine-tuned for 50 epochs, mini-batch size of 24.

4.3.1.6.3 Post processing

The model was trained to classify two classes – dysplasia and no dysplasia. The model output is the probability of dysplasia for each frame. The processing speed of the model was measured on a NVIDIA Tesla T4 graphics processing unit (GPU) and Intel(R) Xeon(R) Central processing unit (CPU). An exponentially weighted moving average of 100 consecutive frames was used to make a diagnosis of dysplasia. This allows a prediction to be made over several consecutive frames.

4.3.1.7 Statistical analysis

Descriptive statistics consisted of the mean (+/- standard deviation). The performance of the CAD system on a per frame level was calculated in terms of accuracy, area under the curve, specificity and sensitivity. A 15-fold cross validation methodology was used to train and assess the performance of the CNN.

4.3.2 - Results

In total 76,496 magnification video frames (47,438 dysplastic, 29,058 non-dysplastic) of BO were analysed by the CNN. Using an automated process, the imaging split of the testing data set was obtained using the labels on the screen. This is summarised in table 14. Frame labelling was not done in this experiment which is why this methodology was used. 52,958 frames were i-

scan3/OE imaging. Of the total 76,496 frames 881 frames had no labels on the screen and so could not be allocated to any subgroup. The remaining 22,657 frames were high-definition white light, i-scan 1 and i-scan 2.

Table 14: The magnification testing data set subdivided based on light modality

Imaging mode	Number of magnification frames
High-definition white light	6877
i-scan 1	11,548
i-scan 2	4232
i-scan3/Optical enhancement	52,958
No labelling	881

The classification threshold is the cut-off point set to assign a predicted classification (dysplasia/no dysplasia). An exponentially weighted moving average of 100 consecutive frames was used to make a diagnosis of dysplasia at a threshold of 0.65. The CNN achieved a sensitivity of 82%, specificity of 82% and area under the curve of 90% (Figure 35). The mean assessment speed per frame was 0.0135 seconds (SD, $\pm$ 0.006).

Figure 35: The CNN achieved an area under the curve of 90% in characterising dysplasia in BO on magnification imaging using any light modality.

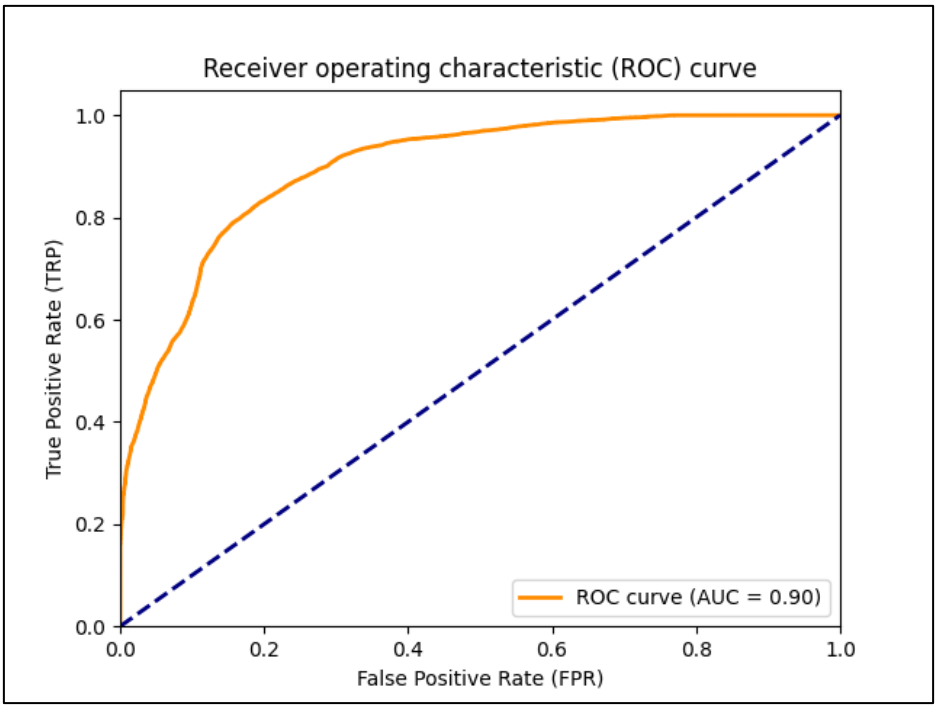


Table 15 shows the results from this model with and without temporal filtering at a threshold of 0.65 reflecting the impact this has on the results.

Table 15: Comparison of the performance of the CNN in characterising dysplasia in Barrett's oesophagus with and without temporal filtering

	Accuracy (%)	AUC (%)	Sensitivity (%)	Specificity (%)
With temporal filtering (100 consecutive frames)	82	90	82	82
Without temporal filtering	81	90	83	77

AUC; Area under the curve

The optimal result from this initial feasibility experiment was using temporal filtering at a threshold of 0.65. The performance of the CNN was assessed at different thresholds which is

summarised in table 16 and 17 which show the results at different thresholds with and without temporal filtering over 100 frames. Table's 15,16 and 17 show the stepwise methodology followed to achieve the optimal initial results in the initial experiment. This allowed a clear understanding of the approach to take when performing the main experiment in section 4.4.

Table 16: Performance of the CNN without temporal filtering at different thresholds

Threshold	Accuracy (%)	AUROC (%)	Sensitivity (%)	Specificity (%)
0.5	81	90	87	73
0.65	81	90	83	77
0.75	80	90	80	80

Table 17: Performance of the CNN with temporal filtering over 100 frames

Threshold	Accuracy (%)	AUROC (%)	Sensitivity (%)	Specificity (%)
0.5	83	90	88	74
0.65	82	90	82	82
0.75	79	90	73	88

In the next section the main points are summarised from this initial experiment, what lessons were learned and changes that were applied leading on to the main experiment in section 4.4 in this chapter.

4.3.3 Strategies that were changed based on the feasibility classification experiment

Several observations were made from this initial experiment to allow for improvements for the main experiment in this chapter. These changes would reflect real world practices, would be more reproducible and generate better results going forwards. The main changes made were:

1- In real world practice expert endoscopists would use chromoendoscopy to assess BO using magnification imaging. In this case with Pentax imaging this would be using i-scan3/OE. In the initial experiments the testing set was composed of all the different images modalities as shown in table 14 in this chapter. Although most frames were i-scan 3/OE. 30% of the total frames in the testing set were not i-scan3/OE. I would ensure that the whole testing set in the main experiment would be composed of chromoendoscopic images which in theory would

improve results as this imaging modalities allows a clearer view of the pit pattern and vascularity on magnification imaging in BO.

2- It would be important to assess the performance of a model in different conditions using different iterations of a testing set again to reflect real world practice. It should be tested on all available i-scan 3/OE frames in the first instance to show the robustness of the model. However, in real world practice magnification imaging would be used in a small part of the oesophagus and on higher quality images. Therefore, two further iterations of the testing set would be generated. First very high quality still images would be extracted to reflect the real-world practice where an endoscopist would freeze a high-quality frame in zoom to assess the vessels and pit patterns and make their own prediction. It would make sense for the neural network to make that prediction at the same time which would fit with the clinical workflow in endoscopy. Another scenario would be to extract a small continuous sequence of frames reflecting the real-world practice where an endoscopist would assess one small area of the oesophagus (small number of continuous sequence of frames) to make a prediction. The AI system in a similar manner and using the principals of temporal filtering used in the pilot study would make a prediction based on these sequences. Using these principles would help see which conditions the AI system would perform best to give the most accurate and optimal predictions of dysplasia.

Using the annotation tool, I created three i-scan3/OE imaging data sets which were labelled differently to test the performance of the CNN in different conditions in preparation for the next phase of experiments – high quality still images, short continuous sequence of frames and all available video frames per case. Therefore, there was three versions of data sets per patient in the next phase.

4.4 Main Experiment – The development of neural networks which can successfully characterise early neoplasia in Barrett's oesophagus on magnification imaging

4.4.1 Methods

4.4.1.1 Patient recruitment, Endoscopic procedures and video collection, tissue acquisition and histology

The same protocol as in the feasibility study in section 4.3 was used for the recruitment of patients, collections of endoscopic videos of magnification imaging and the acquisition of the histology for these cases.

4.4.1.2 Annotation strategy

A different approach was taken with regards to the annotation strategies learning from the lessons of the faesability experiment in section 4.3. Initially like the faesability study in section 4.3 I uploaded videos on to a computer vision annotation tool (Odin vision, London, UK). I used this to annotate the frames as 'dysplasia' or 'no dysplasia' based on the vascular and mucosal pit pattern. The area of annotation matched with the EMR or biopsy histology which was considered the gold standard.

I added a further level of annotation for imaging modality – the annotation was i-scan3/optical enhancement imaging only as this was the data set that would formulate the testing data set. I felt that this would make a significant impact on the results.

In addition, I added further levels of annotations to include high quality image labels and a continuous sequence of image labels (Figure 30). This provided three iterations of the data set:

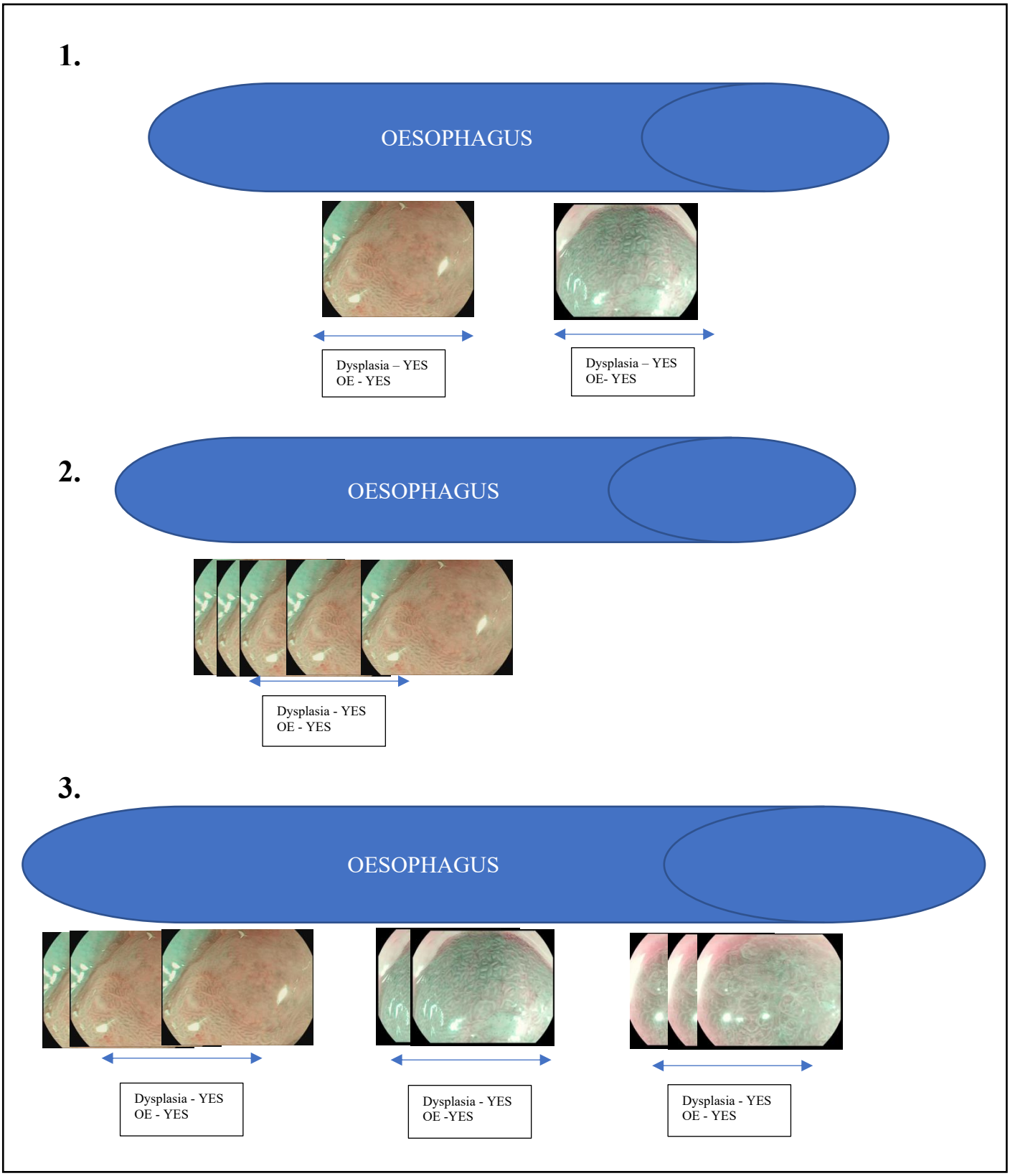
-High quality frames

-Sequence of frames

-All available magnification frames of the oesophagus

The frames were used to train and validate a CNN to be able characterise dysplasia on magnification imaging specifically on chromoendoscopic imaging.

Figure 36: The annotation strategy used to give three iteration of data sets. 1)Annotation of high quality i-scan3/ optical enhancement (OE) magnification frames in the oesophagus, 2) annotation of a single sequence of continuous i-scan3/optical enhancement magnification frames per patient, 3) annotation of all the available i-scan magnification frames per patient



4.4.1.3 Model data set

57 different patients were included (34 dysplastic patients and 23 NDBE patients). The CNN was trained with 60,174 (39,347 dysplasia, 20,827 NDBE) magnification video frames. The training data set included WL, i-scan 1 and i-scan3/OE magnification images (figure 37).

The performance of the CNN was evaluated using a leave-one-out cross-validation methodology. This is a type of cross-validation. The data set is split into training and testing set data. The data for all patients is used for training except for data from one patient which is used for testing. This process is done 57 times, leaving out the data set from a different patient each time which is used for testing the performance of the model.

The test set included all the i-scan 3/OE frames only. This reflected the real-world scenario where an endoscopist would make an optimal assessment of BO using zoom imaging on chromoendoscopy. This was a significant difference from the initial feasibility experiment in section 4.3. Using this training methodology 57 different folds or models were generated. Each fold was trained using all the procedures except one procedure which then becomes the test case for that fold. As a result, the AI system was tested on all available cases.

The testing set included 49,726 i-scan 3/OE magnification frames (14,464 NDBE frames, 35,262 dysplastic frames) (Figure 37).

As discussed earlier in this chapter, three iterations of the testing data set were generated in order to allow for three different levels of results. This would allow for different scenarios to be tested to assess the best way to optimise the performance of the AI system (Figure 36) and determine what clinical workflow to use to optimise performance when used real time in endoscopy:

1- High quality I-scan 3/optical enhancement magnification images
2- Short continuous sequence of i-scan 3/optical enhancement magnification frames per patient
3- All available i-scan 3/optical enhancement magnification frames

4.4.1.3.1 Test set 1 – High quality frames

I randomly selected between 5 and 16 high quality chromoendoscopy from each patient. The final test set consisted of 350 frames (138 NDBE frames, 212 dysplastic frames) from 57 patients (Table 18). This reflects a real-world situation where an endoscopist carefully assesses a single area of the oesophagus and then captures a still high-quality image frame to make an optimal optical diagnosis to help determine further real-time endoscopic management steps.

4.4.1.3.2 Test set 2 – continuous sequence of frames

I annotated a single short continuous sequence of frames per patient for the presence or absence of dysplasia in each video. There was a total of 11,471 i-scan 3/OE magnification frames in this test set from 57 patients (Table 18). The average length of each sequence was 8 seconds per patient.

This reflects the scenario where endoscopists would spend a short period assessing one part of the oesophagus on magnification imaging. The same way that an expert would potentially make better decisions over several frames, this iteration of the test set would allow us to evaluate the AI system whilst allowing for a temporally informed decision.

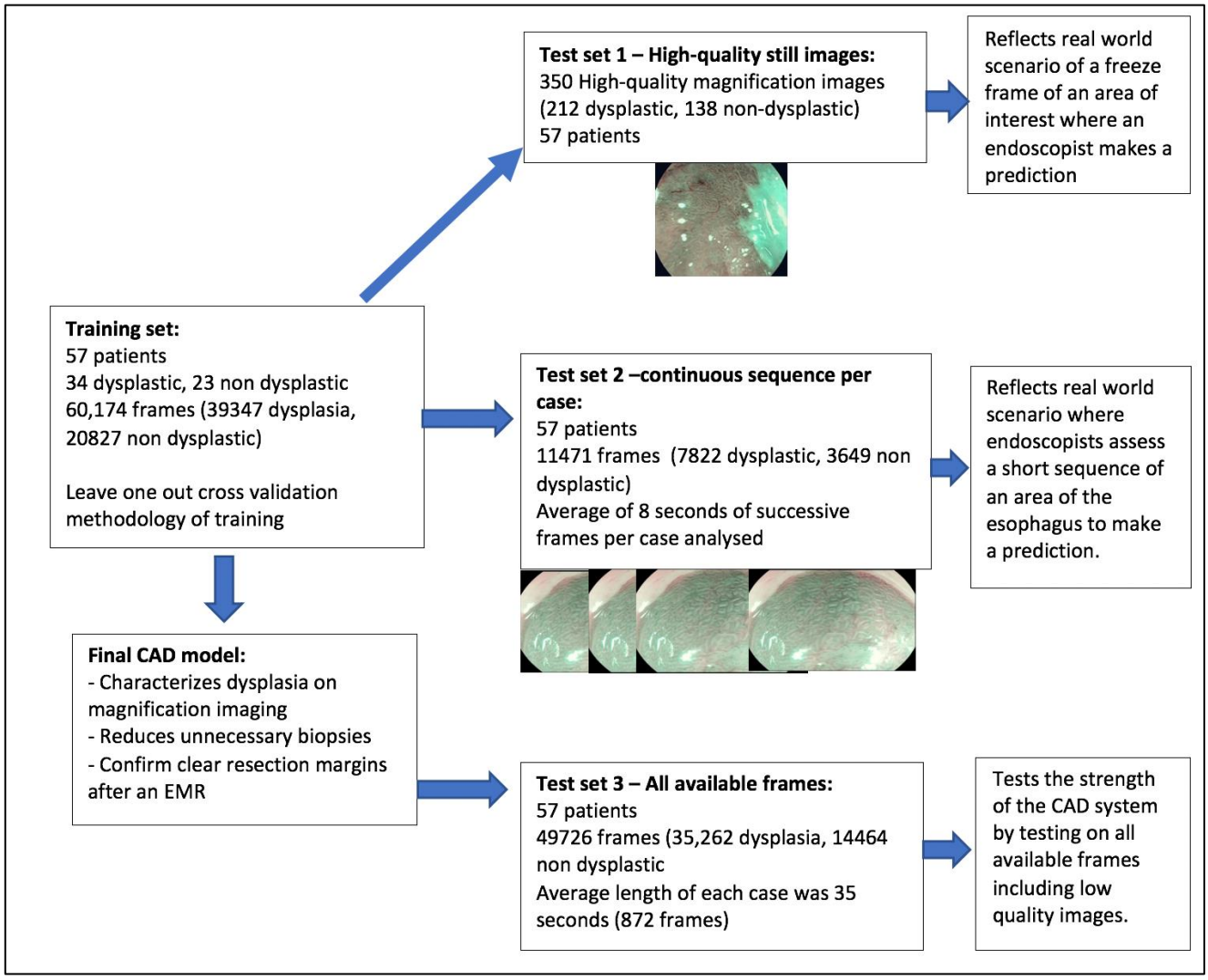
4.4.1.3.3 Test set 3 – All available magnification frames

I included all available magnification i-scan 3/OE frames in each video/patient. There was a total of 49,726 frames in this test set from 57 patients (Table 18). The average length of each of each case was 35 seconds (872 frames per patient).

Table 18: Total number of i-scan 3/OE frames annotated and included in the testing set for each annotation strategy. The testing set in the leave one out cross validation models included i-scan 3/OE frames only.

Type of annotation strategy	Number of patients	Total number of frames	Number of dysplastic frames	Number of non-dysplastic frames
High quality frames (Test set 1)	57 (34 dysplastic, 23 non dysplastic)	350	212	138
Sequence of frames (Test set 2)	57 (34 dysplastic, 23 non dysplastic)	11,471	7822	3649
All available frames (Test set 3)	57 (34 dysplastic, 23 non dysplastic)	49,726	35,262	14,464

Figure 37: Breakdown of the model data set overall for generating a CNN for the characterisation of dysplasia in Barrett's oesophagus. A breakdown of each iteration of test sets which consisted of i-scan3/OE images only in this model



CAD; Computer aided diagnosis, EMR; Endoscopic mucosal resection

4.4.1.3.4 Break down of the data set based on histology and location

Data was collected from four different European centres from four countries (United Kingdom, Spain, Austria and Belgium). As discussed previously there was a total of 57 different patients. 23 had non dysplastic Barrett's oesophagus and the remaining 34 patients had dysplastic Barrett's oesophagus on the corresponding EMR, or targeted biopsy specimen areas assessed with magnification imaging. Table 19 shows the breakdown of the data set based on histology and location of where the procedure was performed.

To generalise the ability of a model to perform in different scenarios I felt it would be important to vary the location and histology of the data set.

Table 19: Breakdown of the data set based on the location of the procedure and the EMR/biopsy histology of the corresponding areas of Barrett's oesophagus assessed with magnification imaging.

	Location				EMR/Biopsy Histopathology		
	United Kingdom	Belgium	Spain	Austria	HGD	IMC	NDBO
Number of patients	30	17	6	4	19	15	23

HGD; High grade dysplasia, IMC; Intramucosal adenocarcinoma, NDBO; non dysplastic Barrett's oesophagus, EMR; Endoscopic mucosal resection

4.4.1.4 Classification convolutional network

4.4.1.4.1 Pre-processing and augmentation

A CNN was trained using a ResNet101 architecture to characterize BO video frames as dysplastic or non-dysplastic using a leave-one-patient-out cross-validation methodology. We trained 57 models on all the procedures except one, which becomes the test procedure for that fold. To ensure generalisation across the data each fold was tested on the same epoch.

Data augmentation was performed randomly to reduce overfitting, including colour transformations (brightness, saturation and hue, contrast) and affine transformations (translation, rotation and scaling). A validation set was used after each training iteration on 5000 images to spot for divergence in the validation loss. For each fold the training parameters were kept the same. Mini-batch training was done where a training iteration is performed with different mini-batches of 5000 images. Images were cropped (removing the black borders) and then resized to 448 x 448 pixels and then the pixel values are normalised. All images from each patient were always in the same set (training or testing) on each iteration to prevent there being any data leakage.

4.4.1.4.2 Hyperparameters and training

The network was pretrained on ImageNet and then fine-tuned on our data. Learning rate: 1e-4, fine-tuned for 6 epochs, mini-batch size 32. The pretrained model was trained using Pytorch, which was also used for training our model. The ImageNet weights are provided in the Pytorch platform.

4.4.1.4.3 Post processing

The model was trained to classify over two classes: dysplastic versus non-dysplastic. The output of the model is the probability of dysplasia for each frame which is a number between 0 and 1 that is then thresholded. On the prediction on the sequence of frames (test set two) an exponentially weighted average of the consecutive frames was used to make a diagnosis of dysplasia. The same threshold of 0.65 was used on each of the three testing sets to maintain consistency and allow for a fair comparison of the three outputs. The processing speed of the model was measured on a NVIDIA GeForce RTX 3090 graphics processing unit (GPU).

4.4.1.5 Statistical analysis

Descriptive statistics consisted of the mean (+/- standard deviation). The performance of the CAD system on a per frame and per patient level was calculated in terms of accuracy, AUC, specificity and sensitivity. A 57-fold leave-one-patient-out cross-validation methodology was used to train and assess the performance of the CNN. 57 folds were required as there were 57 patients in the data set. We trained 57 models on all the procedures except one, which becomes the test procedure for that fold. This process was repeated for each fold.

4.4.2 Results

4.4.2.1 Per frame performance of the CNN

4.4.2.1.1 Test set one – High quality still images

The CNN model was tested on 350 high quality magnification i-scan 3/OE frames. The results per frame was an accuracy of 91%, AUC of 96% (Figure 38), sensitivity of 94% and specificity of 86%.

4.4.2.1.2 Test set two – sequence of frames

This test consisted of 11,471 i-scan 3/OE magnification frames. An exponential weight moving average was used. The performance of the CNN on this test set consisted of an AUC of 96% (Figure 38), accuracy of 90%, sensitivity of 92% and specificity of 84% (Figure 39)

Figure 40 and 41 shows an example of an automated analysis of four video cases with Barrett's dysplasia (Figure 40) and four further examples of automated analysis of videos with no evidence of dysplasia (Figure 41) using the CNN model for magnification imaging. Temporal filtering is used to make the per case prediction. These scenarios show the likelihood of a correct prediction by the CAD system per patient (green line) and also compares the performance to the underlying prediction by the endoscopist (blue line) on the same image. In figure 40 the CNN model correctly predicts the likelihood of neoplasia (blue line) on each frame. This overlaps closely with the per frame prediction of the endoscopist (green line). In Figure 41 the CNN model correctly predicts a zero percent likelihood of dysplasia in this NDBO case.

Table 20 shows a comparison of the performance of the model with and without temporal filtering whilst making a prediction on the sequence of frames in this test set at a threshold of 0.65

Table 20: Comparison of the performance of the CNN to characterise dysplasiaa on the sequences of magnification frames with and without temporal filtering

Temporal filtering?	AUC	Accuracy	Sensitivity	Specificity
No	94%	87%	90%	82%
Yes	96%	90%	92%	84%

AUC; Area under the curve

4.4.2.1.3 Test set 3 – All available frames

The CAD system was tested on all available 49,726 magnification i-scan 3/OE frames. The performance showed a per frame accuracy of 89%, AUC of 95% (Figure 38), sensitivity of 92% and specificity of 82%

Figure 38: Area under the curve analysis of the performance of the CNN on (A) High quality images (B) sequence of frames per case and (C) all available frames

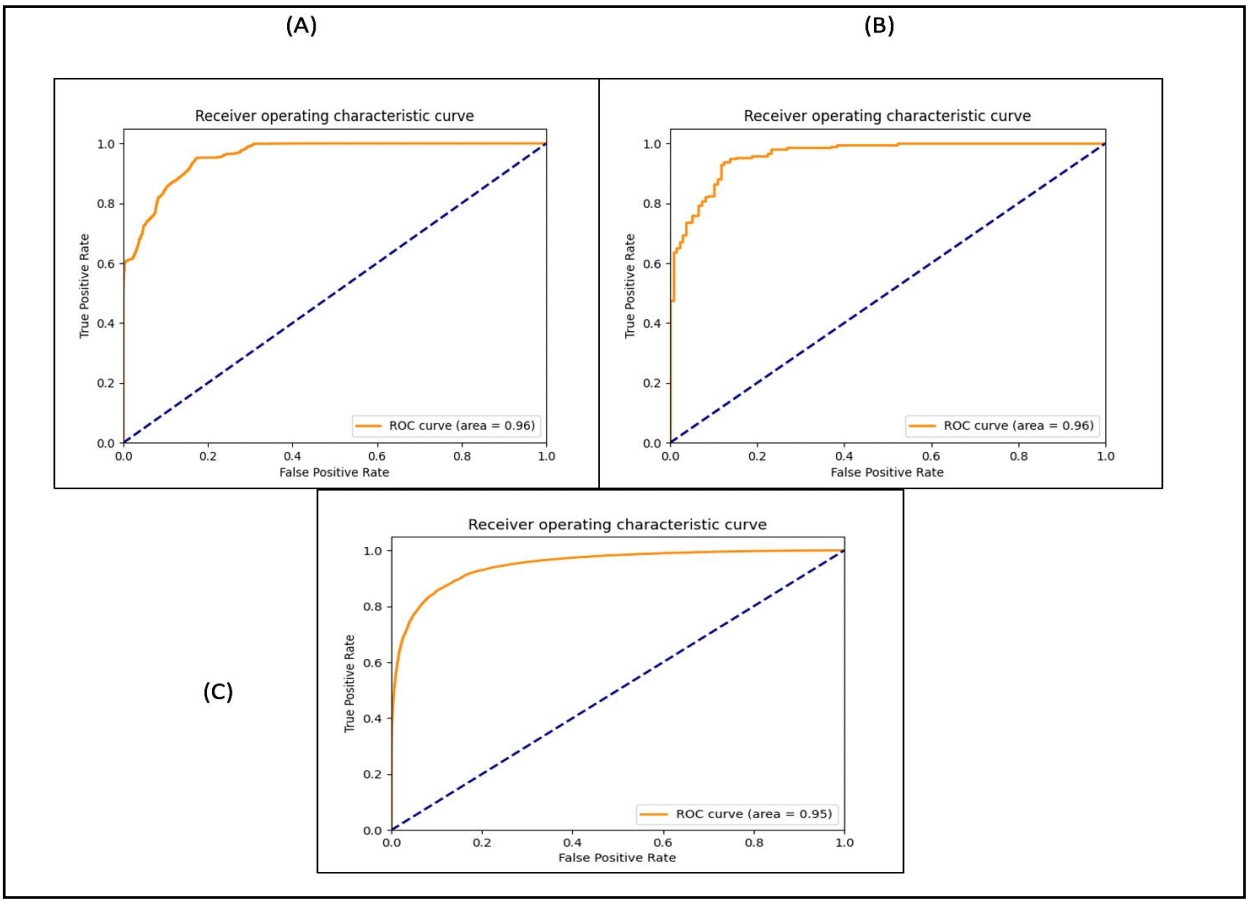


Figure 39: The breakdown of the performance of the CNN on the sequence of frames (test set two) with temporal filtering using a threshold of 0.65. All the frames in the testing set were on i-scan 3/OE imaging modality. There was a total of 11471 i-scan 3/OE frames. FP = 580 False positive frames, TP = 7220 True positive frames, TN = 3069 True negative frames, FN = 602 False negative frames. There were no rejections therefore all the available frames were included.

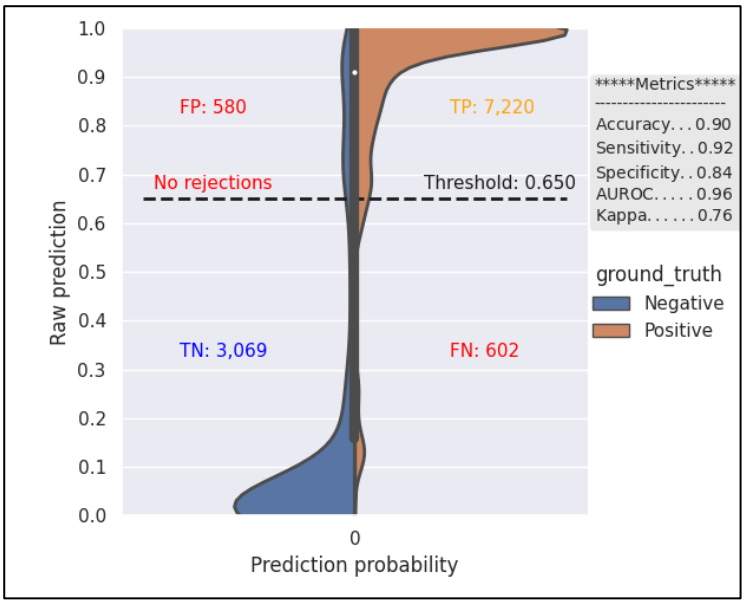


Figure 40: Performance of the CNN in prediction the likelihood of dysplasia on dysplastic images using an exponentially weighted moving average over a consecutive sequence of frames in four different cases. Blue = CNN prediction over several frames using temporal filtering, Green = endoscopist prediction over several frames. Prediction threshold = 0.65 (Red line). The grey dots are each of the individual per frame predictions. Overall, there is good overlap between the endoscopists (Blue line) and CNN (green) prediction which matches the gold standard which is the EMR histology.

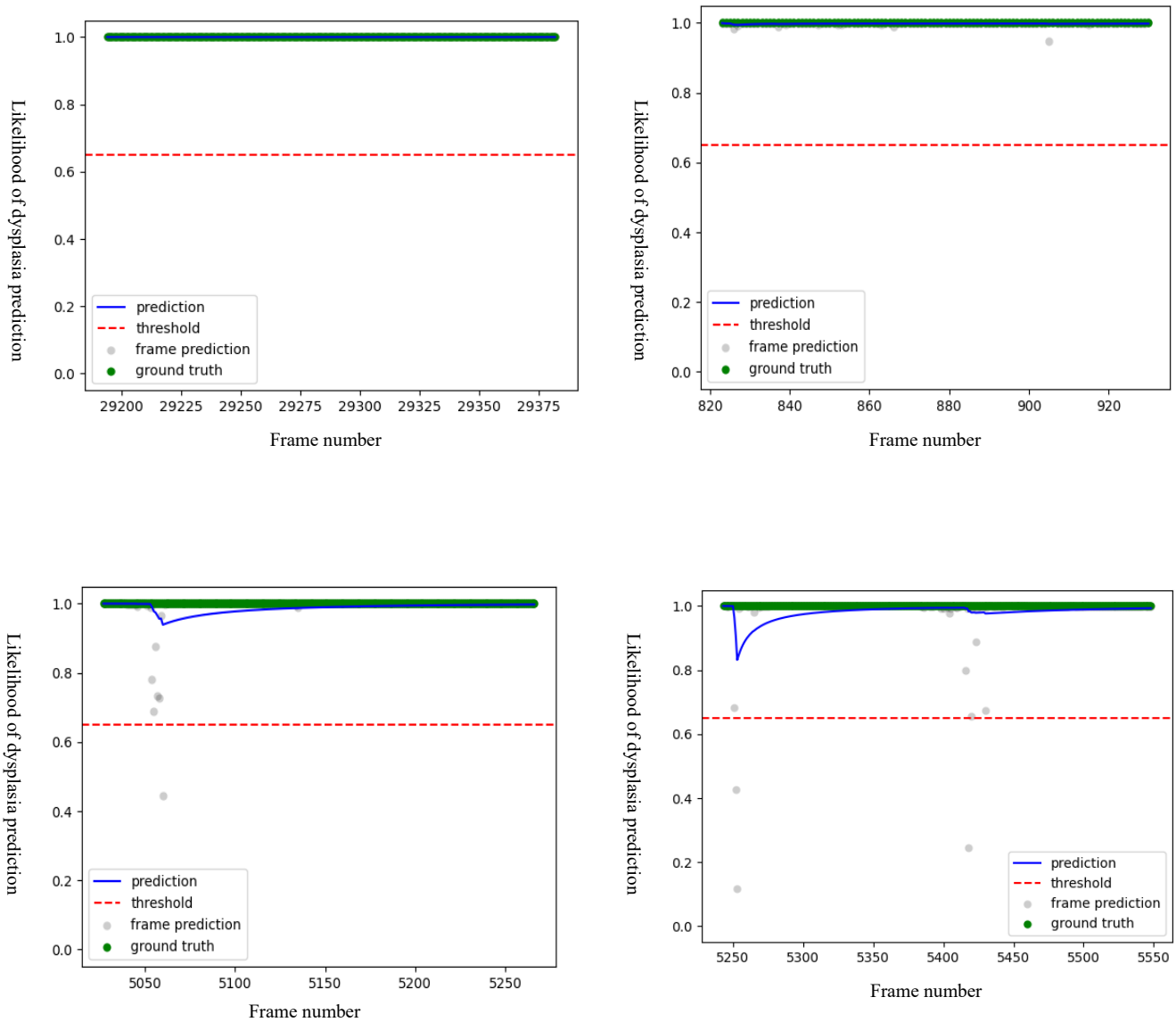
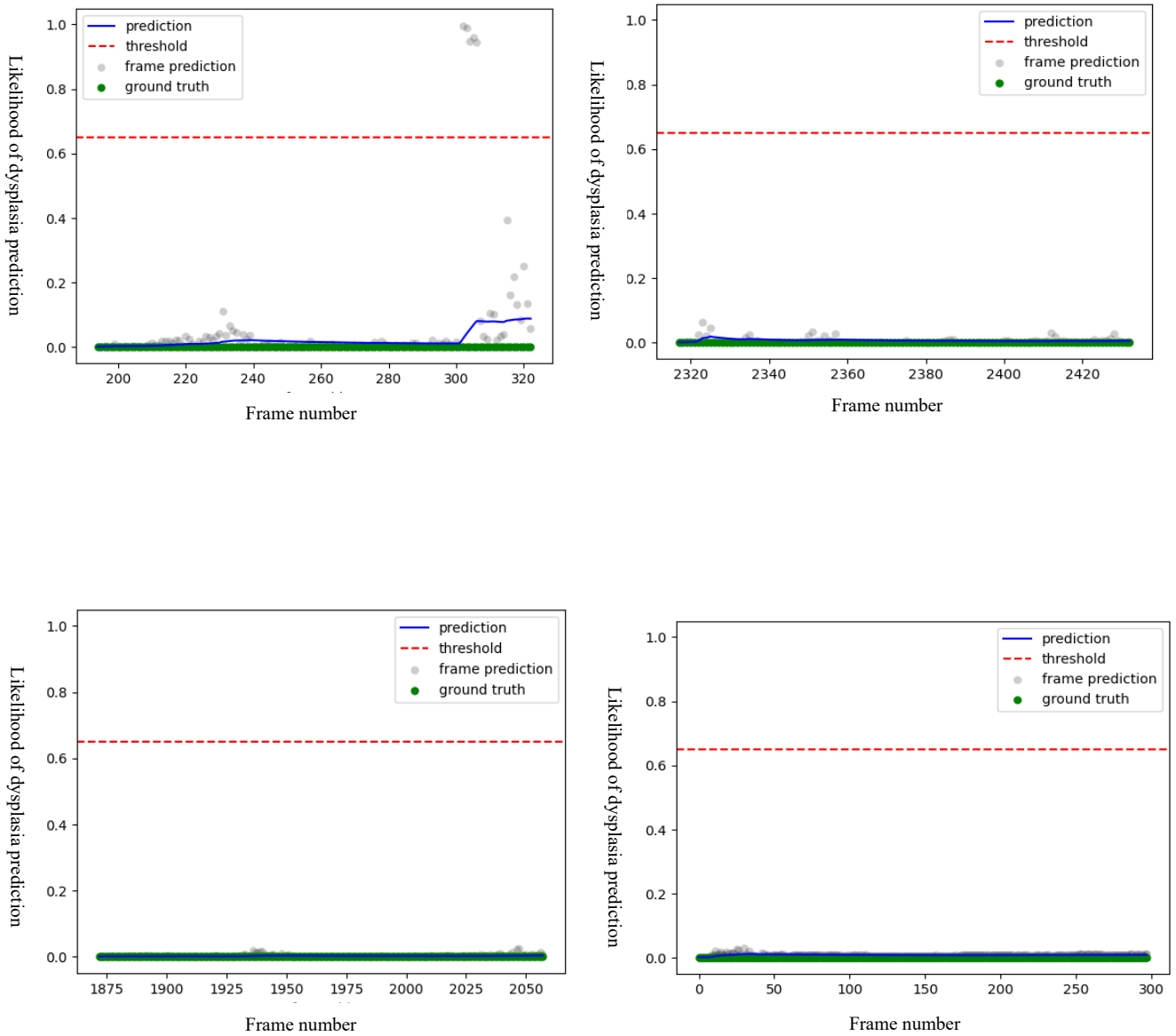


Figure 41:Performance of the CNN in the prediction of the likelihood of dysplasia on images with no dysplasia using an exponentially weight moving average over a consecutive sequence of frames in four different non dysplastic cases. Blue = CNN prediction, Green = endoscopists prediction. Threshold = 0.65 (Red line). The grey dots are each of the individual per frame predictions. Overall, there is good overlap between the endoscopists (Blue line) and CNN (green) prediction which matches the gold standard which is the EMR and/or biopsy histology



4.4.2.2 Per patient performance of the CNN

4.4.2.2.1 Test set two – sequence of frames

There were three different scenarios for a per patient prediction generated based on different prediction thresholds which can be adjusted in an endoscopic assessment by setting different minimal thresholds for a correct per patient prediction (Table 21). A minimum proportion of frames required to be correctly predicted for dysplasia/no dysplasia for a positive diagnosis/negative diagnosis of dysplasia for each patient was set at a threshold 90%, 80% and 70% of frames in each different scenario.

Based on a threshold of greater than 80% of frames in each video being predicted correctly the CNN had a per patient sensitivity of 91% and specificity of 78% in characterising dysplasia. Based on expert consensus 80% was a good threshold to use if we were to embed this into an endoscopic system. It had a balance of a high threshold of frames required to be predicted correctly per patient along with a high accuracy.

Table 21: Per patient performance prediction of the CNN in the prediction of the presence of dysplasia in a continuous sequence of i-scan 3/OE magnification imaging frames

	Minimum percentage of frames in the sequence required to be correctly predicted for dysplasia for a positive diagnosis per patient	Per patient sensitivity
Scenario one	Greater than 90%	85%
Scenario two	Greater than 80%	91%
Scenario three	Greater than 70%	97%

4.4.2.2.2 Test set 3 – all available video frames

The CNN achieved a per patient sensitivity of 91% and specificity of 78% based on a minimum threshold of 70% of the frames per patient being predicted correctly.

Table 22 summarises the performance of the CNN in giving a correct per patient prediction of dysplasia based on different thresholds. Again, this can be adjusted in an AI system depending on the levels of accuracy required to achieve an accurate prediction.

Table 22: Per patient performance prediction of the CNN in the prediction of the presence of dysplasia using all available magnification i-scan 3/OE frames

	Minimum percentage of frames in the sequence required to be correctly predicted for dysplasia for a positive diagnosis per patient	Per patient sensitivity
Scenario one	Greater than 80%	79%
Scenario two	Greater than 70%	91%

4.4.2.3 Performance of the CNN based on histology

4.4.2.3.1 Test set 2 – sequence of frames

As discussed earlier in this section there are a total of 34 dysplastic patients in this experiment. 19 patients had HGD and 15 patients had IMC on histology based on EMR or targeted biopsy.

With the 'sequence of frames' analysis the CNN had a sensitivity of 88% in characterising HGD (3,933 frames out of 4,485 frames were correctly predicted for dysplasia). The CNN has a sensitivity of 99% in characterising IMC (3,287 frames out of 3,337 frames were correctly predicted). As previously discussed, the CNN had achieved a per frame specificity of 84% in the 23 patients with no evidence of dysplasia.

4.4.2.3.2 Test set 3 – all available video frames

The CNN was able to characterise HGD with a sensitivity of 92% (19,924 out of 21,540 frames correctly predicted for the presence of dysplasia). The CNN characterised for IMC with a sensitivity of 92% (12613 out of 13,722 frames correctly predicted). As previously discussed, the CNN achieved a per frame specificity of 82% in the 23 cases with no evidence of dysplasia in BO.

Table 23: The per frame prediction performance of the CNN in characterising dysplasia on magnification imaging based on histology

	Per frame sensitivity (High grade dysplasia) N = 19 patients	Per frame sensitivity (Intramucosal adenocarcinoma) N = 15 patients	Per frame specificity N = 23 patients
Test set two – sequence of frames	88% (3933 out of 4485 frames correctly predicted for dysplasia)	99% (3287 out of 3337 frames correctly predicted for dysplasia)	84%
Test set three – all available frames	92% (19,924 out of 21,540 frames correctly predicted for dysplasia)	92% (12613 out of 13722 frames correctly predicted for dysplasia)	82%

4.4.2.4 Diagnosis speed of the CNN

The mean per frame assessment speed of the CNN was 0.0135 seconds (Standard deviation, +/- 0.006) or 74 frames per second.

4.4.3 Discussion

The experiments in this chapter demonstrate a computer aided diagnostic system which can characterise dysplasia on magnification chromoendoscopy with a high accuracy in various scenarios reproduced by creating different iterations of test sets to reflect different real-world scenarios. My aim was to test the ability of the AI system to be able to make a diagnosis of early cancer even in situations where lower quality images were included (test set three – all available video frames). The results in this chapter suggest that this algorithm may therefore be able to potentially work effectively in real-time in endoscopy for characterising early cancer in BO.

As discussed in various sections throughout this thesis thus far, despite advances in endoscopic imaging in the last two decades there is still a significant miss rate of early cancer in BO. Magnification endoscopic imaging in combination with chromoendoscopy is a valuable additional tool in the endoscopic armoury to help optimise early cancer detection rates in BO.

Magnification imaging allows for a much clearer assessment of the vascular abnormalities and pit pattern to allow for a better assessment for the presence or absence of dysplasia. There have been several classification systems developed in a number of published studies to make a more effective diagnosis on this imaging modality. However, the main issues are a lot of these classification systems are considered too complex therefore there is a lack of uptake in its usage in non-expert centres.

The automation of characterisation on magnification imaging with the use of an AI system would potentially help make the process of assessment of BO on magnification endoscopy easier, in turn this would potentially increase the uptake of its use in non-expert centres. Hypothetically training an AI system using magnification imaging is easier than training for detection on overview images like that exemplified in chapter three in this thesis. This would be because the images are clearer, there is less artefact causing false positives and patterns are clear which would allow for easier classification predictions on each frame. It would also be easier to develop a more robust model with stronger results due to the much clearer distinction of what counts for a positive diagnosis. Therefore, it would be ideal to increase the uptake in terms of usage of this modality in more hospitals particularly if used with AI. The added benefit of an AI system on magnification chromoendoscopy is it would allow an expert to more accurately delineate the resection margins during an EMR or ESD therefore maximising the chances of a complete early cancer resection and therefore minimising the risk of requiring surgery further down the line of treatment due to recurrence.

To the best of my knowledge there has been only one other published study which developed a CNN to characterise dysplasia on magnification imaging in BO(129). They had developed a CAD system that was able to characterise dysplasia on NBI magnification images. The study involved data from two European centres. They tested the performance of the algorithm on 183 high quality images. Dysplasia was characterised with an accuracy of 84%, sensitivity of 88% and specificity of 78%. The performance of the algorithm was also tested on NBI zoom videos (30,021 frames). The accuracy, sensitivity and specificity of the CAD per frame were 85%, 75% and 90% respectively(129).

The performance of the CAD system in this chapter was demonstrated on a different imaging system (Pentax) therefore it is difficult to make a direct comparison between the two studies. However, the performance of the CAD system in the final experiment in Section 4.4 was higher

on a larger number of frames. On 49,726 i-scan3/OE magnification frames the AI system achieved an accuracy, sensitivity and specificity of 89%, 92% and 82% respectively. On 350 high quality frames the AI system achieved an accuracy, sensitivity and specificity of 91%, 94% and 86%. What was different in our study was that there was a larger number of European centres (Four versus Two). This would potentially allow for more generalisability in the system being able to work in different scenarios and countries. The ideal model would be able to work across all endoscopic platforms and further studies are needed to assess this.

In chapter three I demonstrate an AI system which can detect dysplasia in BO during a pull through assessment of the oesophagus. As shown in chapter three in the human experiments these detection systems perform better than non-expert endoscopists and that's the target group where such a system would be more relevant and beneficial(127). Once the area of abnormality is detected patients are then referred to a tertiary referral centre for further assessment of the area of abnormality which may involve an EMR or ESD particularly if the histology is HGD or OAC. Magnification imaging combined with AI would be particularly useful here to delineate the margins for an optimal resection. This would ensure that all areas of abnormal tissue are removed and an R0 resection is achieved for patients avoiding the need for future surgery with optimal prognostic outcomes. The AI systems for detection and characterisation can work effectively as part of a two-stage process to optimise outcomes for patients.

The reasoning for having three different iterations of the testing set was to test the performance of the system in different scenarios. There is not one set condition during assessment of the oesophagus. Therefore, each of these scenarios reflected situations when these conditions can easily change:

-The performance of the CNN was tested on high quality images (N =350 frames in the testing set) where the highest quality frames were selected per case. This reflects a scenario where an endoscopist may freeze on an image of a high-quality during magnification assessment to then be able to carefully assess the vascular pattern and mucosal pit pattern to determine the possible histology of the area assessed and whether endoscopic therapy or a targeted biopsy is necessary. The per frame performance of the CNN on this test set was an AUC of 96%, accuracy of 91%, sensitivity of 94% and specificity of 86%.

-The second iteration of the test set were a short continuous sequence of frames per case (N = 11,471 frames in the testing set). This reflects the real-world scenario where an endoscopist

would assess a specific part of the oesophagus to determine whether there is evidence of dysplasia or early cancer. In the same way that an endoscopist performing a BO assessment would make a much better clinical decision by assessing the lesion over several frames, this test set would therefore allow an evaluation with the AI system over several frames and for a temporally informed decision. The per frame performance of the CNN on this test set consisted of an AUC of 96%, accuracy of 90%, sensitivity of 92% and specificity of 84%.

-The final iteration of the test set included all the available magnification frames assessed in the oesophagus including lower quality frames (49,726 frames in the testing set). This would allow us to test how robust the model is with performance metrics using all the available frames in the data. The CNN had a good per frame performance on this test set with an AUC of 95%, accuracy of 89%, sensitivity of 92% and specificity of 82%.

In all three iterations of test sets the frames were all on the i-scan/optical enhancement imaging modality. This again reflects the real-world scenario in that assessments on magnification imaging are usually best performed on chromoendoscopy. This was one of the differences from the feasibility experiment in section 4.3 in this chapter where the testing data set was composed of different imaging modalities. This adjustment was potentially one of the contributing factors to an improvement in the results in the main experiment in section 4.4 in this chapter. Studies have showed improved dysplasia detection on optical enhancement imaging(96) and therefore these results again confirm the advantage of utilising this technology to optimise outcomes with the AI system.

Everson et al(96) showed that neoplasia detection was significantly higher on magnification imaging using optical enhancement versus high definition white light in terms of accuracy (77.9% versus 66.7%), sensitivity (86.3% versus 83.4%) and specificity (71.2% versus 53.6%). Therefore, this supports the methodology used in this chapter to test the performance of the AI system on i-scan/OE as this is the optimal imaging modality to characterise patterns for dysplasia detection in humans therefore a similar outcome is expected with the AI system. Future studies could potentially look at comparing the performance of the AI system on different imaging modalities.

The CNN in this main experiment was trained using multiple video frames and included all the different types of i-scan imaging modalities as part of the training. This would potentially

maximise the ability of the network to work effectively in different scenarios and environments. This was one of the reasons three different iterations of test sets were generated and that is to allow for this hypothesis to be tested. Training was done using a leave-one-out cross validation methodology. Due to the subtle nature of these lesions and the limited data set available, models that are trained with different train/validate/test splits can potentially generate results that significantly vary therefore implying a degree of statistical uncertainty around the estimated performance. If an experiment has a low performance, it would be difficult to know if the model did not learn a good enough representation. This is why a decision was reached to use a leave-one-out cross validation methodology such that all patients can be evaluated separately using a model as close as possible to training with the whole data set. This model allows us to very effectively be able to see the potential of the model with limited data(196).

The CAD system was able to diagnose dysplasia on magnification image frames with speeds of 0.0135 seconds per frame (Standard deviation, +/- 0.006). This is equivalent to approximately 74 frames per second. In the only other similar study at the time of publishing the work in this chapter, Struyvenberg at al (129) showed a CAD system that characterised dysplasia on magnification NBI frames with speeds of 0.026 seconds per frame. However, to be able to fairly compare the speed of different systems they would need to be benchmarked on the same machine. The results of the speeds from the experiments in this chapter do support the ability of this AI system to be able to potentially work in real time and support the decision making of endoscopists during assessment on magnification imaging.

The histology of the dysplastic patients was HGD and IMC. The model was able to perform well in all the histology subsets in this experiment. In future studies it would be important to test the performance on LGD. As shown in chapter 2 often in LGD there is interobserver variations between histologists and a lot of these patients can be downstaged to NDBE. The use of AI and magnification imaging could therefore potentially help with this problem.

A particular strength of the experiment was including cases of varying histology and from various centres (four). This would potentially allow the system to better perform in different clinical settings and in different countries. This can only be truly tested in a prospective trial in the endoscopy unit.

The magnification CAD system would fit in as part of a two staged algorithm (figure 42):

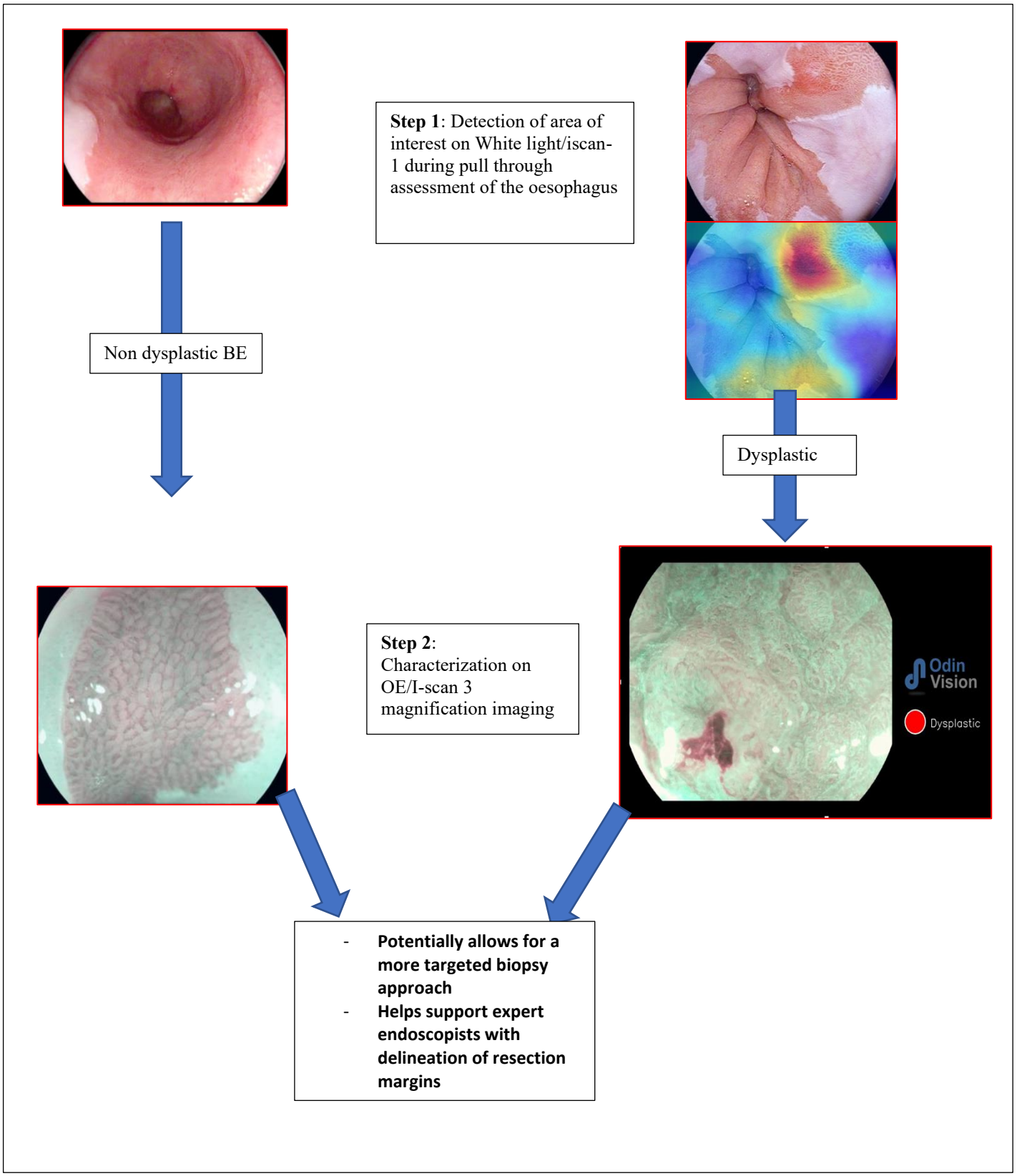
1- Stage one: AI system for detection of suspicious areas during a pull through assessment of the oesophagus on either white light or i-scan 1 imaging. This would be done using the model described in the experiment in chapter 3. This step would be relevant to all units performing Barrett's surveillance and the importance of this step is to maximise detection of early cancer during routine Barrett's assessments.

2- Step two: AI system for the characterisation of dysplasia on magnification imaging as described in this chapter. Once step one of the AI model picks up an abnormality step two can further characterise the area of abnormality on magnification imaging. This would help confirm an area of dysplasia and allow for a targeted biopsy. In an expert centre this second step will help serve the purpose of supporting the delineation of the resection margins allowing for an early and complete (R0) curative endoscopic resection.

This two-step algorithm would potentially allow for a more targeted biopsy approach during surveillance endoscopies in non-expert centres. In comparison to Seattle protocol biopsies this would allow for an improvement in terms of costs, patient tolerance of a shorter procedure as well as maximising time for other procedures to be done during the endoscopy session. This final point is particularly important during a time when there are significant backlogs secondary to Covid-19.

This chapter demonstrates a CAD system which can effectively diagnose dysplasia on magnification imaging with high accuracies on both a per frame and per patient level. This would have the potential value in improving patient care by reducing the need for unnecessary biopsies and more accurate endoscopic resections with clear margins. This system would need to be evaluated in a prospective randomised multicentre clinical trial in real time in the endoscopy unit.

Figure 42: Two step algorithm of the AI system in detecting and then characterising dysplasia in BO which in combination would potentially allow for an optimal patient outcome. Stage one uses the detection AI system developed in chapter 3 which detects area of abnormalities on pull through assessments of the oesophagus. Stage two uses the characterisation AI system developed in this chapter to assess any areas of abnormality in further detail or confirm areas of non-dysplastic Barrett's oesophagus.



4.4.4 Study limitations and future work

There were some limitations in the work discussed in ths chapter which I could improve on in future work. This included:

- The CNN was trained on a single endoscopic platform (Pentax). To allow it to work effectively on other endoscopy platforms it would need to be trained on that data set for example Olympus and Fuji. This would allow this AI system to be more generalisable and work in all endoscopy units. In a future study I would first test the performance of this AI system on Olympus and Fujifilm technology. I will show that the performance is poor if not trained on these different data sets and therefore there is a need to train further algorithms with a broader data set which includes all types of endoscopic technologies.

- The system was not benchmarked against endoscopists like I did in chapter 3 in the BO dysplasia detection study. In future studies I would select experts and non-experts to characterise the presence/absence of dysplasia on at least 50 randomly selected magnification images with an equal split of dysplastic/non dysplastic images but placed in a random order. This would help further show the true value of this AI system. On this occasion I would also test against experts unlike in chapter 3 where the AI system was only tested against non-experts. This AI system would have a value for experts in terms of delineating resection margins therefore testing the performance against that cohort would be important.

- The data set was of a limited size of 57 different patients. In future studies I would expand the data set.

- There was no low-grade dysplasia histology included in this study. I wanted to focus first on creating a robust model for detecting HGD and IMC as these have the higher risks of progression. Low grade dysplasia is more difficult to detect and I would need to create a training data set specific for low grade dysplasia in order to build a model that is much more targeted towards this. As shown in chapter 2 there has always been controversy in the diagnosis of LGD in BO and such an AI system will help support the diagnosis if trained with a robust enough data set.

- There is a need for a randomised prospective multicentre clinical trial to validate these findings in real time in the endoscopy setting.

4.5 Summary of the chapter

In this study assessing the performance of an AI system in the characterisation of dysplasia in BO on magnification imaging I demonstrate:

-An artificial intelligence system which can characterise dysplasia on chromoendoscopy magnification frames with a high sensitivity and specificity in different scenarios.

-A CNN which can characterise dysplasia on 350 high quality chromoendoscopy magnification frames with a sensitivity of 94% and specificity of 86%.

-A CNN which can characterise dysplasia on a combined total of 11,471 continuous sequence of chromoendoscopy frames with a sensitivity of 92% and specificity of 84%.

-A CNN which can characterise dysplasia on all available chromoendoscopy magnification frames (49,726 frames) of BO including lower quality images with a sensitivity of 92% and specificity of 82%.

-A CNN which has a high performance in the different histological subsets of cases (high grade dysplasia and intramucosal adenocarcinoma).

-A CNN which demonstrates a high per patient performance for the characterisation of dysplasia in Barrett's oesophagus.

-To the best of my knowledge this is the first published artificial intelligence system for the characterisation of dysplasia in BO using magnification imagea developed using the Pentax imaging system.

4.6 A clinical consequence of early detection: Rising demands for endoscopic therapy and management of associated bleeding complications

With the potential advances in the detection of early cancer in the oesophagus with technologies like the AI technologies discussed in chapters 3 and 4 there will be an increasing need for endoscopic treatments of early cancer. Endoscopic resections offer the benefit of curative resections. The risks are associated bleeding which can be managed with endoscopic haemostatic techniques. The benefits of endoscopic treatments far outweigh risks, and the most important thing is that endoscopists have the tools to manage such complications.

In chapter 5 I discuss work I carried out to assess the use of Haemospray for the management of intraprocedural bleeding post endoscopic therapy in the oesophagus. At the time of publishing the work in chapter 5, to the best of my knowledge, this was the largest study of its kind to look at the use of Haemospray for this indication. It offers an alternative haemostatic strategy to standard of care methods particularly in complex bleeds in difficult locations.

4.7 Reducing the burden of late diagnosis: Artificial intelligence can enhance detection and minimise bleeding complications from advanced oesophageal tumours

As discussed throughout this thesis thus far there are associated miss rates of early cancer in Barrett's oesophagus. This is despite advances in endoscopic technologies over the past two decades. Advanced oesophageal malignancy has several complications associated with it including GI bleeding which can be difficult to manage. Artificial intelligence has the potential to minimise rates of progression by supporting endoscopists with early cancer detection.

However endoscopic strategies are required for UGI bleeding secondary to oesophageal malignancies. These are often difficult to treat with standard endoscopic modalities due to the friable nature of the tumour. In chapter 6 I discuss a study I carried out on the use of Haemospray in malignancy related bleeding. This offers an important alternative strategy for these patients due to its non-contact nature, ease of application and the ability to be applied over a large surface area. At the time of publishing the work in chapter 6 as far as I am aware this was the largest study of its kind.

CHAPTER 5

USE OF TC-325 FOR THE MANAGEMENT OF BLEEDING FOLLOWING ENDOSCOPIC THERAPY IN THE OESOPHAGUS

CHAPTER 5 USE OF TC-325 FOR THE MANAGEMENT OF BLEEDING FOLLOWING ENDOSCOPIC THERAPY IN THE OESOPHAGUS

The work presented in this chapter formed the basis of a peer reviewed publication. Text and some of the figures were adapted for publication. Citation(197):

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At the time of publishing the work in this chapter there was limited small scale studies or case series on this area. The aim was to provide a larger scale study to provide more answers to the role of TC-325 within the GI bleed algorithm for the management of intraprocedural bleeding post endoscopic therapy. Particularly as it is a haemostatic modality that is increasingly being used and there is increasing volumes of endoscopic therapy being performed.

5.1 Introduction

I have shown in chapters 3 and 4 the potential use of artificial intelligence systems for the detection of early oesophageal cancer in BO. This would allow for curative endoscopic therapy to be offered to patients. With advances in endoscopic techniques there are risks of bleeding following endoscopic therapy and there needs to be endoscopic tools in the armoury to be able to manage such bleeds following interventions.

Upper Gastrointestinal bleeding (UGIB) is a significant cause of morbidity and mortality (2% - 17%) worldwide(131). One cause of this is intraprocedural GI bleeding of which there is an increasing incidence particularly with advances and increasing complexity of endoscopic therapy. The rates of bleeding are variable and depend on the underlying treatment. In the case of early oesophageal cancer resection there is a 1-2% risk of bleeding following an oesophageal EMR and 1-6% risk of bleeding following an oesophageal ESD(132).

There are also significant rates of bleeding following endoscopic therapy in other parts of the upper GI tract. Bleeding rates after a gastric ESD vary between 1.8% - 15.6%(198)(199). Bleeding rates following a duodenal EMR vary from 0 – 29%(200). The higher rates of bleeding in the duodenum maybe secondary to the anatomy and increased vascular supply to that area.

There are a number of modalities for management of post endoscopic therapy intraprocedural bleeding including thermocoagulation, mechanical clips and adrenaline injection therapy(130). Dual endoscopic modalities are considered superior to monotherapy in the management of peptic ulcer bleeds(146). However there has been limited data at the time of the study in this chapter on the optimal endoscopic management techniques for post endoscopic therapy intraprocedural bleeding in the oesophagus.

With the ongoing advances in screening and imaging modalities and with the potential advent of AI in the coming years there will be more lesions in the oesophagus which will be detected at an early stage including larger cancerous lesions which carry a higher risk of bleeding complications. Advances in endoscopic resection techniques of EMR and ESD will allow for an en bloc resection and a more accurate histological assessment and most importantly better outcomes for patients(201). This will allow for organ preservation of the oesophagus and avoid the need for an oesophagectomy. Therefore, endoscopists should have methods at their disposal to potentially manage any associated bleeding risks.

TC-325 (Haemospray; Cook Medical, Winston-Salem, North Carolina, USA) is a mineral based haemostatic powder used for the management of GI bleeding. Haemostatic powders have been shown to be safe, simple and effective. TC-325 is able to tamponade any active bleeding in the GI tract for up to 72 hours and it can be applied over a large surface area(202). Once the TC-325 powder gets in contact with the blood, it absorbs the water which then triggers a clotting cascade which then forms a mechanical tamponade across the bleeding site across the GI mucosal surface(203).

TC-325 has potential benefit in the management of post endoscopic therapy GI bleeding after endoscopic treatment in the oesophagus. It can be applied to the resection site under direct vision and the application is non-contact and therefore will minimise any risk associated with contact with the resection area. Heamostatic therapy with direct contact during intraprocedural bleeding may be challenging where access to the bleeding source may be difficult for example at the

gastro-oesophageal junction in the retroflexed position after resection of a lesion which extends into the cardia.

Therefore, as well as working on ways to improve detection of lesions in the oesophagus, we must also continue to work on ways to improve outcomes following endoscopic therapy in this patient cohort such that advanced endoscopic techniques can continue to be offered safely.

5.2 Aims of the study

The main aims of this study were:

- To assess the success of endoscopic haemostasis with TC-325 in patients with uncontrolled intraprocedural bleeding following endoscopic therapy in the oesophagus

- Secondary aim included:
    - To assess the 7 and 30-day rates of rebleeding following TC-325 treatment of intraprocedural bleeding following endoscopic therapy in the oesophagus
    - To assess the 7 and 30-day mortality rate following the treatment of intraprocedural bleeding in the oesophagus with TC-325
    - Compare the performance of TC-325 when used as a monotherapy, combination therapy or rescue therapy in the treatment of intraprocedural bleeding following endoscopic treatment in the oesophagus
    - To assess for any adverse events following TC-325 treatment post endoscopic therapy in the oesophagus
    - Compare the performance of TC-325 in the treatment of intraprocedural bleeding in the oesophagus to treatment of intraprocedural bleeding following endoscopic treatment in the stomach and duodenum.

5.3 Methods

5.3.1 Patient selection criteria and recruitment

An international registry was set up to look at the real-world use of TC-325 in the management of GI bleeding. In this study patients were recruited prospectively from 16 centres in France, Spain, USA and UK between January 2016 and November 2019.

Consecutive patients with active GI bleeding following intraprocedural bleeding in the oesophagus, stomach or duodenum were recruited from each centre. All the endoscopists had training on the use of the device. The decision on use of treatment was left at the discretion of the endoscopist. This would allow for the capture of real-world data that would capture the best possible snapshot of current practice and outcomes with the use of this haemostatic modality.

5.3.2 Ethics

The study had received approval from the London – South East Research Ethics Committee (October 2016) (International Standard Randomised Control Trial Number registry with study ID ISRCTN29594250). The centres in the other centres that participated in the study also received approval from their local authorities. All the patients recruited into the study had provided informed consent. The conduct of the study was in accordance with the principles of the Declaration of Helsinki.

5.3.3 Risk stratification

Patients recruited into the study were scored using both the Rockall and Blatchford Scoring systems for GI bleeding.

The Rockall estimates the risk of mortality or re-bleeding in patients following an upper GI bleed and has been shown to be an accurate predictor of this(204). It combines multiple metrics in order to give this risk including age, heart rate, systolic blood pressure, specific comorbidities and stigmata from the haemorrhage(205). These metrics were incorporated into an online customised database such that the score is automatically calculated for each patient.

The Blatchford score risk stratifies patient to determine those that would need a more urgent intervention and low risk patients that can be managed as an outpatient. Like the Rockall score the metrics required to calculated this were included into the customised database such that the score calculation is automated for each patient.

5.3.4 Device and procedure

A disposable delivery device was used by the endoscopist for the application of TC-325 treatment. The device is composed of a 7-Fr or 10Fr delivery catheter, a syringe which contains the TC-325 powder and an introducer handle which has a built-in carbon dioxide canister which supports the propelling of the powder.

Before inserting the delivery catheter through the endoscope, the endoscope accessory channel is flushed with air. The catheter is then advanced through the accessory channel of the endoscope and under direct endoscopic vision the catheter is held approximately 1-2cm from the site of bleeding without direct contact to the area. The TC-325 powder is then delivered in short bursts with complete coating of the area of bleeding. The endoscopist would then observe the site of bleeding for five minutes to confirm that immediate haemostasis is achieved. If there is failuire of treatment with active ongoing bleeding escalation of therapy is required which is left to the endoscopists discretion.

5.3.5 Definition and study end points

The primary outcome is the immediate endoscopic haemostasis rates following TC-325 application after intraprocedural bleeding post endoscopic therapy in the oesophagus. Secondary outcomes were 7 and 30-day re-bleeding rates, and 7 and 30-day mortality rates following TC-325 application after intraprocedural bleeding post endoscopic therapy in the oesophagus. Other secondary outcomes were complication rates following treatment with TC-325 treatment in the oesophagus. A further secondary objective was to compare the performance metrics following the use of TC-325 after treatment of bleeding following endoscopic treatment in the oesophagus versus bleeding following endoscopic treatment in the stomach or duodenum.

The immediate haemostasis rate was measured after 5 minutes of application of the TC-325 to the site of bleeding. This was decided following a consensus of international experts at the 2015 United European Gastroenterology Week meeting.

Re-bleeding was defined as a haemaglobin drop of more than 2g/L, persistent or new haematemesis, or malaena with significant haemodynamic instability following the initial endoscopy. This was a definition which was previously in other studies and consensus statements and therefore for consistency the same definitions were used(206)(148).

TC-325 could be used as a monotherapy, combination therapy or rescue therapy. These were defined as follows:

- Monotherapy - The use of TC-325 as a single therapy.
- Combination therapy – The use of T C-325 with other conventional modalities (Mechanical clips, adrenaline injection, thermal coagulation)
- Rescue therapy – When conventional modalities (Mechanical clips, adrenaline injection, thermal coagulation) fail to achieve haemostasis with ongoing active bleeding TC-325 is used as a rescue treatment. Following this the site is observed for 5 minutes to confirm immediate haemostasis.

5.3.6 Follow up

All patients were followed up for up to 30 days following the initial endoscopy where TC-325 treatment was applied. The follow up data was obtained from outpatient clinical review, telephone consultations and from patient clinical records.

All the data was inputted into an anonymised and customised database designed specifically to capture all the relevant information from different centres.

5.3.7 Statistics

The occurrence of each outcome was quantified as both a frequency and a percentage. Descriptive statistics was used for the analysis which included the median and the interquartile range (IQR).

5.4 Results

5.4.1 Baseline data and demographics of the overall study population

Between January 2016 and November 2019, a total of 73 patients were recruited that had intraprocedural bleeding following endoscopic treatment in the oesophagus (n = 40), stomach (n = 12) and duodenum (n = 21). 51 patients were male, and 22 patients were female. Patients had a median age of 73 years (IQR, 66 – 80).

The median Blatchford and Rockall score were 5 (IQR, 0 – 9) and 6 (IQR, 5 – 7) respectively. The most common site of intraprocedural bleeding was in the oesophagus (55%) and most bleeding was secondary to an EMR (39/73, 53%).

Table 24 summarises the main demographics from the overall population. Table 25 summarises the most common cause of bleeding from the overall population.

5.4.2 Baseline data and demographics for patients receiving endoscopic therapy in the oesophagus

Between January 2016 and November 2019, 40 patients were recruited into this study had been treated with TC-325 after intraprocedural bleeding following endoscopic treatment in the oesophagus. Most of these patients (N = 27, 68%) were secondary to an EMR in the oesophagus. The next most common cause was ESD in the oesophagus (N =3, 8%)) and biopsy in the oesophagus (N = 3, 8%). The median Rockall score in this group was 6 (IQR, 5 – 7). The median Blatchford score was 2 (IQR, 0 – 8). The median size of the oesophageal lesions was 10mm (IQR, 5 -20mm) (Table 26).

Table 24: Demographics of the overall population

Demographics	Value
Median age, years (IQR)	73 (66 – 80)
Sex	
Male	51/73 (70%)
Female	22/73 (30%)
Blood thinners	
Antiplatelets	7/63 (11%)
Low molecular weight heparin	5/63 (8%)
Anticoagulation	5/63 (8%)
Bleeding location	
Oesophagus	40/73 (55%)
Gastric	12/73 (16%)
Doudenum	21/73 (29%)

Table 25: The most common cause of bleeding in the overall population divided by anatomical location

Cause of intraprocedural bleeding	Number of patients (%)	
EMR (N = 39)	Oesophagus	27/39 (69%)
	Gastric	3/39 (8%)
	Doudenum	9/39 (23%)
ESD (N = 5)	Oesophagus	3/5 (60%)
	Gastric	2/5 (40%)
	Doudenum	0/5
Ampullectomy/Polypectomy (N = 8)	Oesophagus	0/8
	Gastric	2/8 (25%)
	Doudenum	6/8 (75%)
Sphincterotomy (N = 5)	Oesophagus	0/5
	Gastric	0/5
	Doudenum	5/5 (100%)
Biopsy (N = 5)	Oesophagus	3/5 (60%)
	Gastric	2/5 (40%)
	Doudenum	0/5

EMR = Endoscopic mucosal resection; ESD = Endoscopic submucosal dissection

Table 26: Demographics of patients with bleeding following endoscopic therapy in the oesophagus

Demographics	Value
Sex	
Male	33/40 (83%)
Female	7/40 (18%)
Blood thinners	
Antiplatelets	5/34 (15%)
Low molecular weight heparin	3/34 (9%)
Anticoagulants	2/34 (6%)
Size	
Median lesion diameter (mm) (IQR)	10 (5 – 20)

5.4.3 Outcomes in patients with intraprocedural bleeding following endoscopic therapy in the oesophagus

There was an immediate haemostasis rate of 100%. One patient had a re-bleed. There were no 30-day mortalities. There were no complications associated with the use of TC-325 following intraprocedural bleeding in the oesophagus.

13 cases had TC-325 treatment as a monotherapy, 21 cases as part of a combination therapy and 6 cases had TC-325 treatment as a rescue therapy. The only case of re-bleed was when TC-325 treatment was part of a combination therapy with mechanical clips. The re-bleeding occurred within 24 hours of the index endoscopy where intraprocedural bleeding occurred following an EMR in the oesophagus. The patient had a repeat endoscopy after a day. Table 27 summarises the outcomes in the subgroups within this patient cohort subdivided based on the method of application of TC-325 treatment.

Table 27: Outcomes of treatment with TC-325 during intraprocedural bleeding post endoscopic treatment in the oesophagus in the different subgroups subdivided based on method of application of TC-325

	Monotherapy (N = 13)	Combination therapy (N = 21)	Rescue therapy (N = 6)
Median Blatchford score (IQR)	2 (0 – 6)	3 (0-9)	0 (0 -2)
Median Rockall score (IQR)	6	6 (5-7)	5 (4-6)
Immediate haemostasis (%)	13/13 (100%)	21/21 (100%)	6/6 (100%)
30-day re-bleed (%)	0	1/14 (7%)	0
30-day mortality	0	0	0
Complications from Haemospray treatment	0	0	0

5.4.4 Comparison of outcomes with the treatment with TC-325 following intraprocedural bleeding in the oesophagus versus intraprocedural bleeding post endoscopic treatment in the stomach and duodenum

The median Blatchford score in the oesophageal, gastric and duodenal bleeds were 3, 7 and 3 respectively. The median Rockall score in the oesophageal, gastric and duodenal bleeds were 6, 7 and 6 respectively. There was a 100% immediate haemostasis rate following treatment with

TC-325 in all three cohorts (Oesophagus, stomach and duodenum). There was one 30-day rebleed in the oesophageal cohort and one 30-day re-bleed in the duodenal cohort. There were no re-bleeds in the gastric cohort following treatment with TC-325. The only 30-day mortality was one patient in the gastric cohort. There were no complications with the use of TC-325 in all three cohort of patients.

Table 28 summarises the main outcomes when comparing the use of TC-325 in all three cohorts.

Table 28: Comparison of the outcomes with treatment with TC-325 following an intraprocedural bleed in different anatomical locations in the upper gastrointestinal tract

	Oesophagus	Gastric	Doudenum
Median Rockall score (IQR)	6 (5 – 7)	7 (7 – 8)	6 (4 -7)
Median Blatchford score (IQR)	2 (0 – 8)	5 (5 -7)	7 (3 -9)
Immediate haemostasis (%)	40/40 (100%)	12/12 (100%)	21/21 (100%)
30-day re-bleed (%)	1/30 (3%)	0	1/19 (5%)
30-day mortality (%)	0	1/8 (13%)	0
Complications with the use of Haemospray	0	0	0

IQR = Interquartile range

5.5 Discussion

The data from this study has shown that TC-325 is an effective treatment option if there is bleeding following endoscopic therapy in the oesophagus. With increasing detection of early cancers of the oesophagus for example with AI technology as exemplified in chapters 3 and 4, there will be need for an increasing volume of endoscopic therapy and therefore increased risks of intraprocedural bleeding. Data from 40 patients with bleeding following endoscopic therapy in the oesophagus has shown that TC-325 allowed the achievement of 100% haemostasis in all the case, with re-bleeding in only one case. The median Rockall score in this cohort was 6. This shows that this was a particularly higher risk cohort of patients from teaching hospitals where patients are more complex with potentially more comorbidities and therefore a higher risk of re-bleeding and mortality. The results from this study are compatible with findings from previous studies with smaller sample sizes which have shown TC-325 to be effective in the scenarios of intraprocedural bleeding(207)(208).

ESD is a technique useful for the en bloc removal of any oesophageal lesions which gives it an advantage over EMR where a piece meal resection technique would be required for larger lesions. A large prospective multicentre study which included 181 patients undergoing ESD in the oesophagus (median lesion size, 40mm) showed that delayed bleeding occurred in 1.8% of these cohort of patients(209). TC-325 could have a potential role to be applied at the end of a resection to minimise the risks of a delayed bleed over 48-72 hours after an endoscopic resection particularly for patients that are normally on anticoagulants or antiplatelets. This would need to be studied in a trial to answer and confirm this research question.

Oesophageal EMRs accounted for 68% of intraprocedural bleeds in this cohort versus ESD which accounted for 8% of intraprocedural bleeding in the oesophagus in this cohort. The only re-bleed following endoscopic therapy in the oesophagus was following an EMR which occurred within 24 hours of the index endoscopy. One explanation for this is that an EMR in the oesophagus is relatively uncontrolled in comparison to an ESD. There is no visibility of vessels or the submucosal vascular bed whilst performing a resection. Whereas during an ESD you would have a clear visibility of the vascular bed and better control during a dissection. Diathermy can be carefully applied to the vessels therefore minimising the risk of intraprocedural bleeding.

Intraprocedural bleeding in the oesophagus can be technically challenging to managing with standard treatments requiring contact for treatment. This may be due to the narrow calibre of the oesophagus which can cause views to be obscured particularly with contractions of the oesophagus. There is also a potential higher risk of perforation with direct contact treatment in the muscularis propria layer in an area of a post resection defect. Another issue in the oesophagus would be accessibility for example following a resection of a gastro-oesosphageal junction lesion extending into the cardia. Access if there is a bleed in this area may need to be applied in retroflexion which may be challenging with direct contact haemostatic modalities. It can also be very easy to lose views following a brisk bleed. TC-325 would be useful in overcoming all these challenges and will also allow for an immediate haemostasis in the scenario where there is loss of control of a brisk bleed. The non-contact nature of applying TC-325 means a lower risk of a complication in the post resection defect.

In this study there were no complications associated with the application of TC-325 in the oesophagus. This would provide reassurance in applying the treatment following endoscopic

therapy with minimal concern about a possible perforation at the area of the resection base. A study reviewed a publicly available database to look at reported adverse events for use of TC-325 between 2018 and 2022 in the United States. There was 28 patient related adverse events including perforation, mucosal injury and bleeding. This is for use of TC-325 in GI bleeding of various aetiologies. On careful review by the authors, it was identified that TC-325 was not directly associated with leading to these events. Most reported bleeding episodes were re-bleeding episodes following a failure of initial haemostasis with TC-325. No perforation was directly related to the use of TC-325(210).

The data in this study shows that TC-325 achieved a haemostasis rate of 100% when used as part of a combination therapy in treating intraprocedural bleeding in the oesophagus. This would be potentially useful in scenarios where there is brisk bleeding following an EMR for example with obscuring of view. TC-325 can be applied to achieve control. Once the surface has been coated with the white powder the endoscopist can observe the area for the appearance of a red spot suggesting the site of arterial bleed. The endoscopist can then assess the area and the bleeding can be targeted with a second endoscopic modality such as coagulation, mechanical clips and/or adrenaline injection.

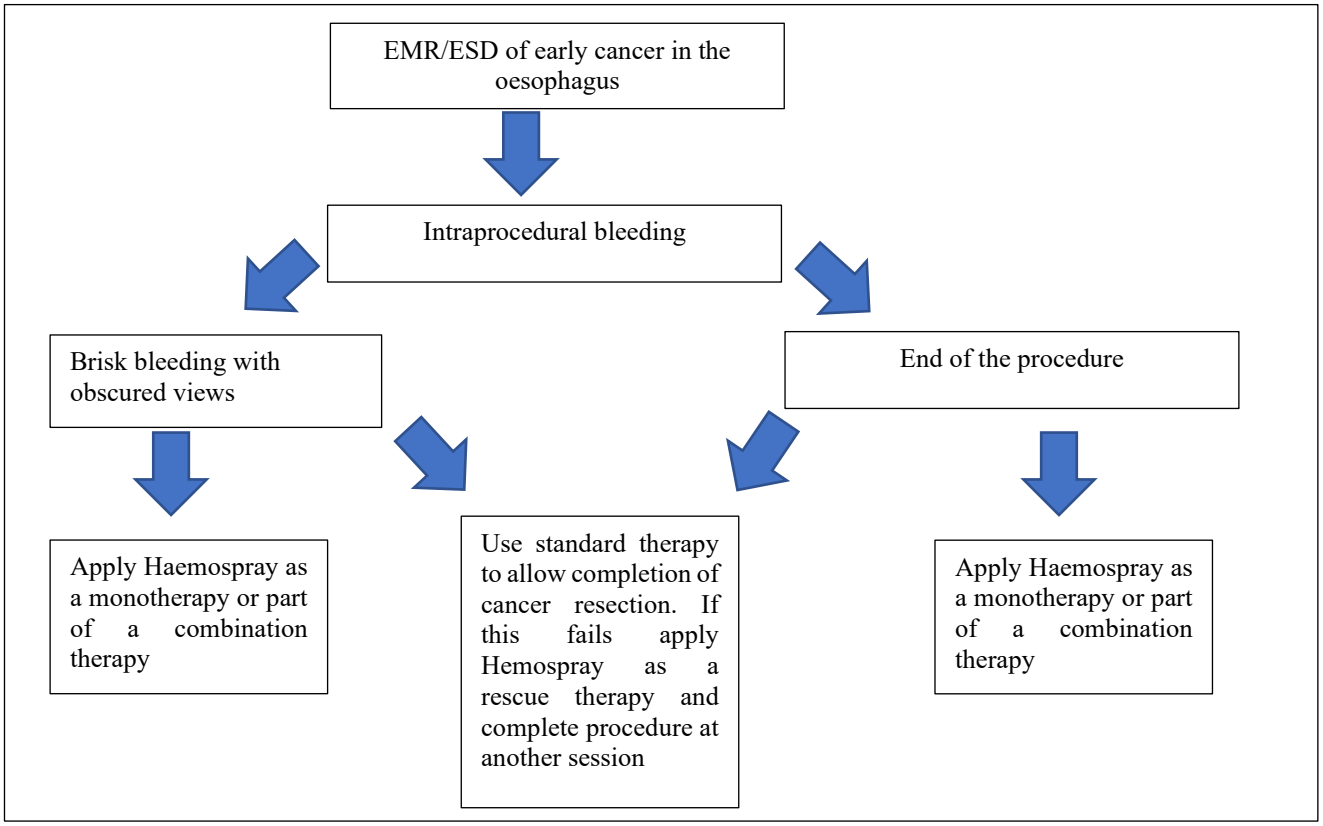
Use of other haemostatic modalities such as clips in a post resection area can pose a potential issue particularly in a resection in an area of BO. These patients would need to return for further treatment of the area with radiofrequency ablation which can be a potential issue if there is still a clip in the area. Also, clips can potentially have an impact on the healing process and contribute to scarring making further endoscopic therapy more difficult. It can also affect further assessment of the area and obscure views in future endoscopies when assessing for any recurrence of neoplasia. TC-325 would normally come off the mucosa after a number of days making any further endoscopic intervention easy to perform if required(211).

One potential issue that can be foreseen with the use of TC-325 during intraprocedural bleeding in the oesophagus is that if it is required in the middle of endoscopic therapy then it would be difficult to continue with completion of the procedure at that point. It may be a better option to utilise other standard endoscopic modalities to allow completion of the resection. The use of TC-325 would be more ideal for the end of the procedure.

The study shows that TC-325 is also affective following intraprocedural bleeding in the stomach and duodenum with an equally effective immediate haemostasis rate of 100%. The median Rockall scores were 7 and 6 in the gastric and duodenal cohort respectively reflecting a higher risk cohort of patients recruited from teaching hospitals similar to the oesophageal cohort of patients. There was one re-bleed in the duodenal cohort following treatment of an intraprocedural bleed post EMR. This may be due to the increased arterial blood supply in the duodenum which would make it more prone to further delayed re-bleeds(200).

There are no clear international guidelines on the management of intraprocedural bleeding following endoscopic therapy in the oesophagus. Based on the data from this study we have made a proposal of a potential clinical algorithm of where TC-325 would potentially fit in the management of these patients (Figure 43). At the end of a procedure TC-325 may have potential role as a first line therapy of treatment. It may also play a role in patients that would need to restart anticoagulants following a procedure with some mild oozing. It can potentially be a bridge whilst anticoagulation is restarted to minimise delayed oesophageal bleeding although this would need a specific study to prove the potential clinical utility of using TC-325 in this way. If bleeding were to occur in the middle of the procedure and further endoscopic intervention was required to remove areas of dysplasia in the oesophagus then it would be best to use coagulation forceps, mechanical clips or adrenaline injection initially to allow the procedure to be completed.

Figure 43: Proposed algorithm for where TC-325 fits into the management of intraprocedural bleeding following endoscopic therapy in the oesophagus



5.6 Study limitations and future research

There were some limitations in the study which I could improve on in future work. This included:

- This was not a randomised control trial. In potential future work I would set up a study comparing the use of TC-325 against other endoscopic modalities to allow a comparison of outcomes.

The first trial option would be to compare TC-325 combined with standard of care haemostatic modalities versus standard of care haemostatic modalities alone in a superiority study. This would be 1:1 randomisation, prospective and multicentre trial. The patient population will include post procedure bleeding following an EMR or ESD in the oesophagus to focus the clinical question. The justification for using combination therapy is because with post endoscopic therapy bleeding there can be visible vessels which would require treatment with coagulation, clips or adrenaline. This study design would assess if the addition of TC-

325 improves haemostasis rates and reduces re-bleeding rates compared to standard of care alone.

The second trial design option would be a prospective randomised control trial where patients that are on anticoagulation are prophylactically treated with TC-325 following an EMR or ESD in the oesophagus. The control group would not have any treatment following the resection. This would be 1:1 randomisation, prospective and multicentre trial. This would answer the important clinical question if TC-325 reduces the risk delayed bleeding following endoscopic therapy in the oesophagus and whether there is an added benefit in applying to specific patient groups on anticoagulation and therefore minimising the risk of delayed bleeding.

-The decision on whether to use TC-325 was left at the discretion of the endoscopists in order reflect a real-world snapshot on the use of Haemospray in these scenarios. The limitation is that this would potentially contribute to a degree of selection bias. In future studies I would randomise patients to either TC-325 or another haemostatic modality including other Haemostatic powders.

-There can be a degree of interobserver variation with regards to the definition of immediate haemostasis. One way of overcoming this limitation in future studies is for the procedures to be recorded and then a consensus reached by an expert panel to agree whether immediate haemostasis had been achieved. This would allow all results to be standardised. Pittayanon et al (212) overcome this by recruiting independent endoscopists to review photo's or videos to confirm treatment failuire of achieving haemostasis in malignancy related bleeding. I would adopt a similair approach for both successful and failed treatments in a future randomised control trial.

- The reason why an endoscopist decided to use TC-325 was not included in the customised database entry. In future studies this would be an important metric I would include to gain an understanding of why endoscopists would use haemostatic powders and in what scenarios rather than other standard haemostatic modalities.

- There are now other Haemostatic powders that have been introduced. It would be important in a future study to have direct comparison between TC-325 and these other Haemostatic

powders. A retrospective study of 56 patients showed that UI-EWD achieved a 96% immediate haemostasis rate in non variceal upper GI bleeding (213). A multicentre randomised control trial of 216 patients showed that Endoclot was non inferior to standard of care modalities in achieving immediate haemostasis in peptic ulcer bleeding (214).

- A potential important future study would be to examine the role of TC-325 in minimising the risk of delayed bleeding on patients that are on anticoagulants or antiplatelet. The research question would be if TC-325 can be used as a bridge in the first 72 hours after the index endoscopy to allow patients to restart their anticoagulation/antiplatelet medications safely and minimise any risk of delayed bleeding.

5.7 Summary of the chapter

In this study I assess the performance of TC-325 in achieving haemostasis during an intraprocedural bleed following endoscopic therapy in the oesophagus. With increasing availability of early cancer detection tools, the volume of curative endoscopic therapy offered in endoscopy units will increase. Therefore, there must be available endoscopic tools to be able to manage any possible bleeding complications that may occur. I demonstrate:

- TC-325 is an effective haemostatic powder for the treatment of intraprocedural bleeding following endoscopic therapy in the oesophagus. There were a 100% immediate haemostasis rates.

- There is a low re-bleed rate. Only one patient had a re-bleed following an oesophageal EMR.

- TC-325 is safe to use in the oesophagus following endoscopic therapy. There was no complication rates associated with its usage.

- TC-325 is also effective when used following intraprocedural bleeding in the stomach and duodenum with low re-bleed rates.

CHAPTER 6

USE OF TC-325 FOR THE MANAGEMENT OF UPPER GASTROINTESTINAL BLEEDING SECONDARY TO OESOPHAGEAL CANCER

CHAPTER 6 USE OF TC-325 FOR THE MANAGEMENT OF UPPER GASTROINTESTINAL BLEEDING SECONDARY TO OESOPHAGEAL CANCER

The work presented in this chapter formed the basis of a peer reviewed publication. Text and some of the figures were adapted for publication. Citation(215):

Hussein M, Alzoubaidi D, O'Donnell M, de la Serna A, Bassett P, Varbobitis I, Hengehold T, Fernandez-sordo JO, Rey JW, Hayee B, Despott EJ, Murino A, Graham D, Latorre M, Moreea S, Boger P, Dunn J, Maine I, Mullady D, Early D, Ragunath K, Anderson J, Bhandari P, Goetz M, Keisslich R, Coron E, de Santiago E, Gonda T, Gross S, Lovat LB, Haidry R. Hemostatic powder TC-325 treatment of malignancy-related upper gastrointestinal bleeds: International registry outcomes. J Gastroenterol Hepatol 2021; 36 (11): 3027 – 3032.

As discussed in chapter 5 with the introduction of more screening tools and the potential increasing use of AI technologies in the coming years as discussed in chapters 3 and 4 there will be increasing detection rates of early cancer in BO. However, on the other side of the spectrum this chapter will discuss what could happen if these oesophageal cancers are not detected early. If oesophageal cancer is not detected early, then advanced oesophageal cancers can bleed which is associated with an increased mortality rate. This is why AI will play a key role as despite advances in endoscopic technology in the last two decades there is still a significant miss rate of early cancers. AI can be the additional factor that can potentially offset some of these miss rates and avoid the potential complications associated with advanced oesophageal malignancy. This chapter will discuss the role that TC-325 can play in treating upper GI bleeding secondary to oesophageal cancer and I will compare this to the management of GI bleeding secondary to tumours of the stomach and duodenum.

At the time of publishing the work in this chapter there was small scale studies or case series on this area. The aim was to provide a larger scale study to provide more answers to the role of TC-325 within the GI bleed algorithm for the management of malignancy related bleeding. Particularly as it is a haemostatic modality that is increasingly being used.

6.1 Introduction

Oesophageal cancer related bleeding accounts for approximately 5% of all upper GI bleeds and often occurs due local invasion of the tumour causing vascular damage(133)(216). The friable and diffusely bleeding tumour surface often makes these patients a difficult cohort to treatment. Other additive factors which contribute to these difficulties are the co-morbidities and underlying clinical frailty. These combination factors contribute to a high failuire rate in endoscopic haemostasis with haemostatic methods which would require direct contact with the oesophageal tumour surface(216).

Endoscopy is the first line treatment option for the management of oesophageal cancer related GI bleeding. Due to fragility of the tumour surface and the diffuse nature of bleeding there is variable haemostasis rates with standard endoscopic modalities which can be as low as 40% and there are associated re-bleed rates of up to 30% following an index endoscopy(217).

Endoscopy normally does not provide a definitive option for the management of GI bleeding secondary to an oesophageal tumour. However, it can help potentially improve transfusion requirements for patients and therefore improve quality of life by minimising re-admissions to hospitals for a blood transfusion. More definitive management can often be provided by radiotherapy or surgery however in the setting of an acute GI bleed secondary to an oesophageal malignancy they may not be as useful. Surgery can be associated with an increased mortality rate and radiotherapy is more useful in the setting of subacute blood loss. Embolisation is associated with a high re-bleed rate(218).

Endoscopic management of an oesophageal malignancy related GI bleed is often a bridge towards definitive treatment which can be in the form of surgery or radiotherapy treatment. Low level blood loss and the associated anaemia can prevent this patient cohort from having the necessary oncological treatment required for their underlying condition. Studies have shown an up to 65% increase in mortality secondary to cancer in patients with an underlying malignancy(219).

As discussed in chapter 5 TC-325 (Haemospray; Cook Medical, Winston-Salem, North Carolina, USA) is a mineral based haemostatic powder used for the management of GI bleeding. Haemostatic powders have been shown to be safe, simple and effective. TC-325 is able to

tamponade any active bleeding in the GI tract for up to 72 hours and it can be applied over a large surface area(202). Once the TC-325 powder gets in contact with the blood, it absorbs the water which then triggers a clotting cascade which then forms a mechanical tamponade across the bleeding site across the GI mucosal surface(203).

Current American guidelines recommend the use of haemostatic powders which are non-contact for the endoscopic treatment of diffuse malignancy related GI bleeding. Oesophageal malignancy related bleeding would fall within this category.

An aim of this chapter is to show if Haemospray is an effective haemostatic modality for oesophageal malignancy related bleeding. This work will highlight the importance of early detection of cancer such that curative endoscopic therapy can be offered. If not detected early they will progress with poor 5-year survival outcomes and associated complications including GI bleeding.

6.2 Aims of the study

The main aims of this study were:

- To assess the immediate haemostasis rates following the treatment of oesophageal malignancy related GI bleeds with TC-325

Secondary aims were

- To assess the 30-day re-bleed rate following the treatment of oesophageal malignancy related bleeding with TC-325
- To assess the 30-day mortality rate following the treatment of oesophageal malignancy related bleeding with TC-325
- To compare the outcomes of patients with gastric/duodenal malignancy bleeds versus oesophageal malignancy related bleeds treated with TC-325
- To assess the effect of TC-325 treatment on transfusion requirement in all sub cohort of patients

6.3 Methods

6.3.1 Patient selection criteria and recruitment

All consecutive patients with an upper GI malignancy related bleed were recruited from 17 centres in the United States, United Kingdom, Germany, France and Spain between January 2016 and March 2020. All patients had received informed consent.

6.3.2 Ethics

The study had received approval from the London – Southeast Research Ethics Committee (October 2016) (International Standard Randomised Control Trial Number registry with study ID ISRCTN29594250). The centres in the other countries that participated in the study also received approval from their local authorities. All the patients recruited into the study had provided informed consent. The conduct of the study was in accordance with the principles of the Declaration of Helsinki.

6.3.3 Risk stratification

Patients recruited into the study were scored using both the Rockall and Blatchford Scoring systems for GI bleeding.

The Rockall estimates the risk of mortality or re-bleeding in patients following an upper GI bleed and has been shown to be an accurate predictor of this(204). It combines multiple metrics in order to give this risk including age, heart rate, systolic blood pressure, specific comorbidities and stigmata from the haemorrhage(205). These metrics were incorporated into an online customised database such that the score is automatically calculated for each patient.

The Blatchford score risk stratifies patient to determine those that would need a more urgent intervention and low risk patients that can be managed as an outpatient. Like the Rockall score the metrics required to calculate this were included into the customised database such that the score calculation is automated for each patient.

6.3.4 Device and procedure

A disposable delivery device was used by the endoscopist for the application of TC-325 treatment. The device is composed of a 7-Fr or 10Fr delivery catheter, a syringe which contains the TC-325 powder and an introducer handle which has a built-in carbon dioxide canister which supports the propelling of the powder.

Before inserting the delivery catheter through the endoscope, the endoscope accessory channel is flushed with air. The catheter is then advanced through the accessory channel of the endoscope and under direct endoscopic vision the catheter is held approximately 1-2cm from the site of bleeding tumour without direct contact to the area. This is a particularly important step due to the fragility of the tumour surface meaning any direct contact may exacerbate bleeding. The TC-325 powder is then delivered in short bursts with complete coating of the area of bleeding. The endoscopist would then observe the site of bleeding for five minutes to confirm that immediate haemostasis is achieved. If there is failure of treatment with active ongoing bleeding escalation of therapy is required with other treatment modalities which is left to the endoscopists discretion.

6.3.5 Definition and study end points

The study definitions for immediate haemostasis, re-bleeding and use of TC-325 as monotherapy, combination therapy or rescue therapy are the same definitions described in chapter 5, section 5.3.5.

The immediate haemostasis rate was measured after 5 minutes of application of the TC-325 to the site of bleeding. This was decided following a consensus of international expert at the 2015 United European Gastroenterology Week meeting.

Re-bleeding was defined as a haemaglobin drop of more than 2g/L, persistent or new haematemesis, or malaena with significant haemodynamic instability following the initial endoscopy. This was a definition used previously in other studies and consensus statements and therefore for consistency the same definitions were used(206)(148).

TC-325 could be used as a monotherapy, combination therapy or rescue therapy. These were defined as follows:

- Monotherapy - The use of TC-325 as a single therapy.

- Combination therapy – The use of TC-325 with other conventional modalities (Mechanical clips, adrenaline injection, thermal coagulation)
- Rescue therapy – When conventional modalities (Mechanical clips, adrenaline injection, thermal coagulation) fail to achieve haemostasis with ongoing active bleeding TC-325 is used as a rescue treatment. Following this the site is observed for 5 minutes to confirm immediate haemostasis.

The transfusion requirements for each case were calculated by measuring the number of units of blood transfused per patient 3 weeks before the procedure, and the number of units of blood transfused for 3 weeks after the procedure starting from immediately after the procedure performed with TC-325 application. The transfusion requirements were calculated when TC-325 was applied as a monotherapy, part of a combination therapy and as a rescue therapy.

The physical status and comorbidities of patients were assessed using the ASA physical status classification with a grading from one to five. ASA status of one means the patient is in good health with increasing severity of co-morbidities with an increasing score.

6.3.6 Follow up

All patients were followed up for up to 30 days following the initial endoscopy where TC-325 treatment was applied. The follow up data was obtained from outpatient clinical review, telephone consultations and from patient clinical records.

All the data was inputted into an anonymised and customised database designed specifically to capture all the relevant information from different centres.

6.3.7 Statistics

For all binary outcomes the occurrence of each outcome was quantified as well as the percentage of patients within each outcome which occurred. A corresponding confidence interval was calculated using the exact binomial method.

The factors associated with each of the outcomes was assessed. For all the binary outcomes this analysis was performed using logistic regression. The separate association between each factor and the corresponding outcomes was assessed separately in univariate analysis. Multiple logistic

regression was performed to adjust group differences for factors that were found to be associated with the outcomes in the first stage of the analysis.

A continuous scale was used to measure the change in transfusion requirements. This was calculated by measuring the difference in the number of units of blood transfused 21 days before endoscopic treatment and 21 days after endoscopic treatment with TC-325. Initially the change in units of blood between the two time periods was examined. The changes in values were approximately normally distributed, and therefore the paired t-test was used at this stage of the analysis.

6.4 Results

6.4.1 Baseline data and demographics of the overall study population

105 patients with an UGI malignancy related bleed were enrolled into the study between January 2016 and March 2020. The median age was 71 (IQR, 60 – 98) years of age. 67% of patients were male. The median overall Rockall score was 8 (IQR, 7-9) and median Blatchford score was 10 (IQR, 7 – 12). 30 out of 105 (29%) cases had an oesophageal malignancy, 69 out of 105 (66%) cases had a gastric malignancy and 6 out of 105 (6%) patients had a duodenal related malignancy. 81 out of 105 (77%) cases were oozing bleeds, 13 out of 105 (12%) cases had a visible vessel/adherent clot and 6 out of 105 (6%) cases were spurting bleeds. The overall median size of lesions was 25mm (IQR, 12-44). 12% of patients were on antiplatelets and 17% of patients were on anticoagulation. 42% of patients had an ASA physical classification of 3, 22% of patients had an ASA physical classification of 4 and 1% of patients had an ASA physical classification of 5.

6.4.2 Baseline data and demographics for patients with oesophageal malignancy related bleeding

30 patients were recruited and treated with TC-325 following an oesophageal malignancy related UGI bleed. The median age was 75 (IQR, 64-70) years of age. 83% of patients were male. The median Blatchford score in this cohort was 10 (IQR, 7 – 12) and median Rockall score was 8 (IQR, 7 – 9). The median size of the oesophageal lesions was 20mm (IQR, 5 – 42.5mm).

6.4.3 Outcomes of treatment with TC-325 in the overall study population

Immediate haemostasis was achieved in 102 out of 105 (97%) patients following treatment with TC-325. A median number of 8 applications of TC-325 were required to achieve haemostasis. In the 3 patients that did not achieve immediate haemostasis, one patient was treated with further endoscopic sessions of argon plasma coagulation and the other two patients were managed conservatively.

Re-bleeding occurred in 13 out of 87 (15%) patients within 30 days of treatment with TC-325. Out of the 13 patients that had a re-bleed 3 patients had a repeat endoscopy withing 30 days of index treatment with TC-325. One of the 3 patients had a repeat treatment with TC-325 on day 26 following index endoscopy. In the remaining two patients there was no bleeding on the repeat endoscopy and no further endoscopic therapy was required. All-cause mortality within 30-days of index treatment with TC-325 occurred in 18 out of 90 patients (20%).

Twelve patients had a repeat endoscopy within 30 days of index treatment with TC-325. In eight patients there was no evidence of bleeding on the repeat endoscopy. In the remaining four patients, one patient had further treatment with TC-325, one patient had further treatment with argon plasma coagulation, one patient went on to have surgery and the remaining patient was managed conservatively.

70 out of 105 (67%) patients were treated as a monotherapy with TC-325, 26 out of 105 patients (25%) were treated with TC-325 as part of a combination therapy and 9 out of 105 patients (9%) were treated with TC-325 as a rescue therapy. Table 29 summarises and compares the outcomes in the monotherapy, combination and rescue therapy cohort.

Mortality and re-bleeding date were missing in 15 patients.

Table 29:Comparison of outcomes in the monotherapy, combination therapy and rescue therapy group following treatment with TC-325 after a malignancy related bleed

Variable	Monotherapy (N = 70)	Combination therapy (N = 26)	Rescue therapy (N = 9)
Immediate haemostasis	70/70 (100%)	23/26 (88%)	9/9 (100%)
Rockall score	8 (IQR, 7-9)	8 (IQR, 7-9)	7 (IQR, 6-9)
Blatchford score	10 (IQR, 7-12)	10 (IQR, 7-13)	12 (IQR, 10-13)
30-day re-bleed	9/62 (15%)	3/17 (18%)	1/8 (13%)
7-day mortality	4/62 (6%)	0	0
30-day mortality	14/62 (23%)	4/20 (20%)	0

IQR; Interquartile range

6.4.4 Outcomes of treatment in oesophageal malignancy related GI bleeds

28 out of 30 patients (93%) achieved immediate haemostasis following treatment with TC-325. 17% of patients had a re-bleed within 30 days of treatment. There was an all-cause of mortality of 8% within 7 days and all-cause mortality of 36% within 30 days of index treatment with TC-325 (Table 30).

6.4.5 Comparison of outcomes of treatment in oesophageal malignancy related GI bleeds versus gastric/duodenal malignancy related GI bleeds

99% of patients with a gastric malignancy related UGI bleed achieved immediate haemostasis following treatment with TC-325. 14% of patients with a gastric malignancy had a re-bleed within 30 days versus 17% in the oesophageal malignancy cohort. There was an all-cause 30-day mortality of 15% in patients with a gastric malignancy related bleed following treatment with TC-325 versus 36% in the oesophageal cohort. 40% of patients in the oesophageal cohort had an ASA of at least 4 versus 21% in the gastric cohort. This may be a contributory factor to the higher mortality rate

Table 30 summarises and compares the outcomes in the oesophageal, gastric and duodenal cohort.

Table 30: Comparison of outcomes in the oesophageal, gastric and duodenal cohort following treatment with TC-325

Variable	Oesophageal malignancy (N = 30)	Gastric malignancy (N = 69)	Doudenal related malignancy (N =6)
Haemostasis rate	28/30 (93%)	68/69 (99%)	6/6 (100%)
Rockall score	8 (IQR, 7-9)	8 (IQR, 7-9)	8 (IQR, 8-9)
Blatchford score	10 (IQR, 7-12)	10 (IQR, 8-12)	11 (IQR, 8-12)
30-day re-bleed	4/23 (17%)	8/59 (14%)	1/5 (20%)
7-day mortality	2/25 (8%)	2/60 (3%)	0
30-day mortality	9/25 (36%)	9/60 (15%)	0

IQR; Interquartile range

6.4.6 Risk factors for re-bleeding after treatment with TC-325 in the overall cohort

Analyses were performed to assess factors associated with 30-day re-bleeding. The separate association of each factor was examined using univariable analysis (Table 31). There were no factors significantly associated with re-bleeding. Therefore, no further analysis was performed for re-bleeding.

Table 31: Univariable analysis assessing the factors associated with 30-day re-bleeding after treatment of malignancy related bleeding with TC-325

Variable	Category	Re-bleeding n/N (%)	Odds ratio (95% CI)	P-value
Method of usage of TC-325	Monotherapy Combination Rescue	9/62 (15%) 3/17 (18%) 1/8 (13%)	1 1.26 (0.30, 5.59) 0.84 (0.09, 7.68)	0.93
Age (**)	-	-	0.72 (0.44, 1.19)	0.20
Gender	Male Female	9/55 (16%) 4/32 (13%)	1	0.63
Haemoglobin (g/dL)	< 10 >10	12/70 (17%) 1/9 (11%)	1 0.60 (0.07, 5.59)	0.65
Urea (mmol/L)	< 8 >8	5/31 (16%) 8/44 (18%)	1 1.16 (0.34, 3.94)	0.82
Blood pressure	≤ 109mmHg >109mmHg	5/31 (16%) 8/47 (17%)	1 1.07 (0.31, 3.62)	0.92
Antiplatelets/ anticoagulants	No Yes	9/63 (14%) 4/23 (17%)	1 1.26 (0.35, 4.59)	0.72
Lesion site	Oesophagus Stomach Doudenum	4/23 (17%) 8/59 (14%) 1/5 (20%)	1 0.75 (0.20, 2.76)	0.66(#)
Lesion size (**)	-	-	1.05 (0.83, 1.32)	0.69
Blatchford score (*)			1.29 (0.50, 3.33)	0.60
Rockall score	-	-	0.88 (0.62, 1.26)	0.49

(*) Odds ratios reported for a 5-unit increase

(**) Odds ratios reported for a 10-unit increase

(#) Doudenum group omitted from analysis due to small numbers. Comparison between oesophageal and stomach groups only.

6.4.7 Risk factors for 30-day mortality after treatment with TC-325

On univariable analysis Blatchford score and the site of malignancy were associated with a 30-day mortality (P < 0.05) (Table 32). There was evidence of an association between the urea and 30-day mortality which was of a borderline statistical significance (P = 0.05). A 5-unit increase

in the Blatchford score was associated with a 4.6-fold increase in the odds of death within 30 days. The odds of death in the gastric cohort were approximately 3 times lower than in the oesophageal cohort.

Table 32: Factors associated with 30-day mortality on univariable analysis

Variable	Category	Mortality (30 days) n/N (%)	Odds ratio (95% CI)	P-value
Method of usage of TC-325	Monotherapy Combination Rescue	10/62 (23%) 4/20 (20%) 0/8	(~)	0.45
Age (**)	-	-	0.92 (0.60, 1.41)	0.86
Gender	Male Female	13/58 (22%) 5/32 (16%)	1 0.64 (0.21, 2.00)	0.44
Haemoglobin (g/dL)	< 10 >10	15/72 (21%) 2/10 (20%)	1 0.95 (0.18, 4.95)	0.95
Urea (mmol/L)	< 8 >8	3/32 (10%) 13/46 (29%)	1 3.81 (0.99, 14.7)	0.05
Blood pressure	≤ 109mmHg >109mmHg	9/34 (26%) 8/47 (17%)	1 0.57 (0.19, 1.67)	0.31
Antiplatelets/ anticoagulants	No Yes	12/59 (20%) 1/18 (6%)	1 0.23 (0.03, 1.91)	0.17
Lesion site	Oesophagus Stomach Doudenum	9/25 (36%) 9/60 (15%) 0/5	1 0.31 (0.11, 0.92)	0.04
Lesion size (**)	-		0.87 (0.69, 1.11)	0.28
Blatchford score (*)			4.60 (1.57, 13.5)	0.005
Rockall score	-		1.15 (0.82, 1.61)	0.42

(*) Odds ratios reported for a 5-unit increase

(**) Odds ratio reported for a 10-unit increase

(~) Unable to calculate odds rations due to no deaths in one category. Analysis using Fisher's exact test

(#) Doudenum group omitted from analysis due to small numbers. Comparison between oesophageal and stomach groups only

6.4.7 Transfusion requirement outcomes following treatment with TC-325 in the overall cohort

There was a significant reduction in the number of units of blood transfused when comparing after and before treatment with TC-325 (Table 33). The mean reduction was 1 unit of blood per patient following treatment with TC-325. Transfusion data was missing for 32 patients.

Table 33: The effect of treatment with TC-325 on the number of units of blood transfused following an upper GI malignancy related bleed

	Number of patients	Number of units of blood transfused Mean +/- SD	Change in units of blood Mean (95% CI)	P-value
In the period three weeks before TC-325 treatment	73	2.5 +/- 2.0	0	P < 0.001
In the period three weeks after TC-325 treatment	73	1.5 +/- 2.5	-1.0 (-1.6, -0.4)	

SD; standard deviation, CI; confidence interval,

A similar significant reduction in blood transfusion requirements was seen when TC-325 was used as a monotherapy. There was a mean reduction of 1 unit of blood per patient following treatment of malignancy related upper GI bleeds with TC-325 (Table 34).

Table 34: The effect of treatment with TC-325 as a monotherapy on the number of units of blood transfused following an upper GI malignancy related bleed

	Number of patients	Number of units of blood transfused Mean +/- SD	Change in units of blood Mean (95% CI)	P-value
In the period three weeks before TC-325 treatment	45	2.3 +/- 2.0	0	P < 0.05
In the period three weeks after TC-325 treatment	45	1.4 +/- 2.5	-0.9 (-1.6, -0.1)	

SD; Standard deviation, CI; Confidence interval

Univariable analysis showed that only the number of units of blood transfused in the 3-week period before the application of TC-325 was strongly associated with a reduction in the number of units of blood transfused. There was some evidence of a difference between genders which was of borderline significance. No other factors were significantly associated with a reduction in the number of units of blood transfused in these patients (Table 35).

Table 35: Univariable associations with the reduction in the number of units of blood transfused following treatment of a malignancy related bleed with TC-325

Variable	Category	Number of units of blood reduction Mean +/- SD	Coefficient (95% CI)	P-value
Number of units of blood transfused before TC-325	-	-	0.5 (0.2, 0.8)	< 0.001
Method of usage of TC-325	Monotherapy Combination Rescue	0.9 +/- 2.5 1.2 +/- 2.9 1.6 +/- 2.1	0 0.3 (-1.1, 1.8) 0.7 (-1.2, 2.6)	0.72
Age(**)	-	-	0.1 (-0.3, 0.6)	0.62
Gender	Male Female	0.7 +/- 2.7 1.9 +/- 2.1	0 1.2 (-0.1, 2.5)	0.06
Haemaglobin	< 10 >10	0.9 +/- 2.8 1.5 +/- 1.7	0 0.6 (-1.1, 2.3)	0.46
Urea	< 8 >8	0.6 +/- 2.7 1.3 +/- 2.7	0 0.7 (-0.7, 2.1)	0.31
Blood pressure	≤ 109mmHg >109mmHg	1.1 +/- 3.0 0.8 +/-2.5	0 -0.3 (-1.6, 1.0)	0.65
Antiplatelets/anticoagulants	No Yes	1.5 +/- 3.1 1.0 +/- 1.6	0 -0.5 (-2.1, 1.2)	0.56
Lesion site	Oesophagus Stomach Doudenum(#)	0.8 +/- 2.5 1.1 +/- 2.7 1.5 +/- 2.4	0 0.3 (-1.1, 1.7) -	0.69
Lesion size(**)	-	-	0.0 (-0.2, 0.3)	0.82
Blatchford score(*)	-	-	0.0 (-1.0, 1.0)	0.95
Rockall score	-	-	-0.1 (0.5, 0.3)	0.65

(*) Regression coefficients reported for a 5-unit increase
(**) Regression coefficients reported for a 10-unit increase
(#) Duodenum group omitted from analysis due to small numbers. Comparison between Oesophageal and Stomach groups only

6.5 Discussion

The study in this chapter shows that there is a high immediate haemostasis rate of 97% and a re-bleed rate of 15% in the 105 patients presenting with an upper GI malignancy related bleed and treated with TC-325.

TC-325 provides a bridging option towards more definitive radiotherapy or surgery for these patients. They are particularly useful in tumour related bleeding as it can be sprayed over a large tumour surface and can be used for tumours that are in difficult positions(133).

Malignancy related bleeding is difficult to treat with standard endoscopic treatment modalities. This is due the fragility of the tumour surface and therefore any contact with this can exacerbate further bleeding. This is also due to the large tumour surface area. Malignancy related bleeds often lead to frequent admissions into hospital and an increase in blood transfusion requirements. There is intermittent oozing from the surface of these tumours as a result of angiogenesis(220). Argon plasma coagulation was an option for treating tumour related bleeding however there was several disadvantages associated with this endoscopic modality in this scenario. It would require multiple treatment sessions and it is not an effective method for treating a large tumour surface area. A retrospective study of 25 patients looking at the treatment of malignancy related bleeding with APC showed an initial haemostasis rate of 73% and a 30-day re-bleed rate of 33% which is less than the outcomes in the study in this chapter(221). The advantages TC-325 would have over APC in this scenario is that is non-contact and can effectively be sprayed over a large area over the tumour surface.

The study in this chapter of 105 patients reflects the largest study known to date looking at the use of TC-325 in malignancy related tumoural bleeding. In the next largest study, there was a cohort of 79 patients with UGI malignancy-related bleeds. There was an immediate haemostasis rate of 97.7% in the overall patient cohort (UGI and lower GI malignancy) and a re-bleed rate 27.3% all of which were in the UGI malignancy related bleeds. Other studies like the study in this chapter show a high immediate haemostasis rate following treatment with TC-325. A randomised control trial showed of 20 malignancy related bleeds showed an immediate haemostasis rate of 90% in the TC-325 group versus 40% in the standard of care group. The 180-day re-bleeding rate was 20% in the TC-325 group versus 60% in the cohort treated with standard

endoscopic modalities(222). A study of 10 patients showed a 30-day re-bleed rate of 30% in the group treated with standard endoscopic modalities versus 10% in the TC-325 group(134).

The outcomes in the oesophageal cohort were worse than that of the gastric cohort. The 30-day mortality rate was significantly lower in the gastric cohort (15%) versus 36% in the oesophageal malignancy cohort. This can be at least partly explained by the differences in the survival rates and prognosis with each malignancy. The 5-year survival rate in gastric malignancy is approximately 21% versus 16% in oesophageal malignancy(223). Following palliative treatment of oesophageal cancer the median survival time is 3-6 months(224). In the cohort in our study 40% of patients in the oesophageal cohort had an ASA of at least 4 versus 21% in the gastric cohort. This may also be a contributory factor to the higher mortality rate. The mortality rates in malignancy overall would need to be considered when reflecting these figures. A separate study of 20 patients showed that most of the patients died at 6 months due to the underlying poor prognosis(222). However, the key point is that immediate haemostasis rate in these cancer cohorts after treatment with TC-325 for the bleed is high therefore providing a potentially effective bridge towards surgery or radiotherapy. It also has as shown in the results in this chapter provided an improvement of transfusion requirements which is important in patients who are being managed with a palliative approach.

In our study the outcomes in the TC-325 combination group were worse than that of when TC-325 is used as a monotherapy. The immediate haemostasis rate in the monotherapy cohort was 100% versus 88% in the combination therapy group. The 30-day re-bleed rate in the monotherapy group was 15% versus 18% in the combination therapy group. One potential reason for these differences is that the use of standard endoscopic modalities on the already fragile tumour surface may disrupt it further. The outcomes in the monotherapy group including the improvement in transfusion requirements with the use of TC-325 as a monotherapy suggests that it could potentially be used a first line monotherapy in the treatment of these patients and a bridge towards radiotherapy or surgery. There is a clear need for large a randomised control trial comparing TC-325 monotherapy versus combination therapy to more clearly define its role in the GI bleed algorithm and more specifically for the treatment of malignancy related bleeding.

The median Blatchford and Rockall score in the study in this chapter were 10 and 8 respectively. This reflects that this was a higher risk cohort of patients with comorbidities from tertiary centres. Based on these scores the predicted re-bleed and mortality rate is 40% and outcomes were lower

than this in the study. One has to take into account that there have previously been studies which have shown that the Rockall scoring system is a useful tool for predicting mortality rates but is not as useful for predicting re-bleeding rates(225).

One of the important results shown from the study is that TC-325 significantly improves transfusion requirements ($P<0.001$). This shows that it potentially slows down any bleeding. This has two main benefits. It helps provide a bridging option towards other more definitive treatments and would be of benefit for patients who are being managed conservatively and who can therefore be discharged. There are studies which have shown that anaemia is often associated with a reduced quality of life in patients with cancer. I have looked at the transfusion requirements 3 weeks before index treatment with TC-325 as that is the critical time period just before and during an acute admission during which blood loss occurs and I looked at the transfusion requirements during a similair time period after the index endoscopy. A pilot randomised trial showed 40% of patients treated with TC-325 received blood transfusions versus 70% of patients treated with conventional endoscopic modalities which supports the findings in our study. A limitation of this outcome in this chapter is that I looked at short term transfusion requirement outcomes

There were no reported complications associated with the use of TC-325 in malignancy related bleeding in our study.

The data from this chapter provides evidence supporting the use of TC-325 for malignancy related upper GI bleeding. Since the work on this chapter has been published a systematic review of four randomised control trials has supported the findings from this chapter. This included 227 patients and has shown that haemostasis was significantly higher with TC-325 compared to standard of care in malignancy related bleeding(226).

In conclusion that data from the study in this chapter shows that TC-325 has a potential important role within the GI bleed algorithm for the management of upper GI malignancy related bleeding including oesophageal cancers. It has a high immediate haemostasis rate; reasonable re-bleed rates and significantly improves transfusion requirements. Its advantages are that it is non-contact and therefore does not disrupt the fragile tumour surface and can be used over a large surface area in a short space of time.

This chapter reflects the potential complications of not detecting oesophageal cancer early. AI will be one of the potentially important early detection tools to allow for early detection and curative endoscopic therapy and therefore prevent progression of disease. It is important to have endoscopic tools in the armoury to manage such complications of malignancy and the data in this chapter shows that TC-325 potentially offers one of these options.

6.6 Study limitations and future research

There were some limitations in the study which I could improve on in future work. This included:

- This was not a randomised control trial. There is a need for a large-scale multicentre randomised control trial comparing TC-325 versus conventional endoscopic modalities for the management of malignancy related GI bleeding. There is also a need for a trial to compare the use of TC-325 as a monotherapy versus combination therapy in upper GI malignancy related bleeding.

  I think the evidence favours the use of monotherapy haemostatic agents in malignancy related bleeding the oesophagus. An randomised control trial has shown better outcomes using TC-325 compared to standard of care modalities (216).

  In a future randomised control trial, I would focus on comparing TC-325 versus other haemostatic powders that are currently available rather than standard of care modalities (coagulation, clips, adrenaline injection, APC). A clinical problem an endoscopists faces is deciding which haemostatic powder to use. There is also no consensus for this due to lack of sufficient evidence. The patient population would include oesophageal, gastric and duodenal malignancy patients. The primary outcome would be immediate haemostasis rates. Secondary outcomes would include 30-day rebleeding rate, 30-day mortality rate secondary to the underlying malignancy and transfusion requirements (30 day, 3 months and 6 months). In this trial design I would focus on looking at improvements in both short- and long-term transfusion requirements to see which haemostatic powders would give more of a lasting benefit and minimises readmissions to hospital with bleeding. This would then potentially guide societies and endoscopy units regarding the best haemostatic powders to apply in these scenarios.

- Justification for the use of TC-325 in each scenario was not included in this study. In a future study it would be useful to include a section in the registry to explain the reasoning behind the use of TC-325 in each scenario where it is used as a monotherapy instead of standard endoscopic modalities. This would help further understand the perceived advantages for the use of TC-325 for endoscopists.

- Longer term transfusion data is needed. In the study in this chapter, 3 weeks before and after index endoscopy with the use of TC-325 was looked at. Longer term data would be helpful to understand any longer-term benefits particularly in patients managed conservatively. Included in this should be further data looking at the number of hospital admissions before and after the index endoscopy and the number of endoscopic procedures which would tie in with the transfusion requirements. This data would be included in future registries.

- Data on the direct cause of mortality for each patient was not included. This will be included in future registries to understand if there were any deaths directly because of GI bleeding. In most of the cases mortality is likely secondary to the underlying poor prognosis of the malignancy and/or secondary to co-morbidities. Most patients had an ASA score of at least 3 and the median score was 8 which would support this argument. However, this does not give a certainty on mortality rates secondary to bleeding.

- Another limitation is I only looked at 30-day mortality in the study in this chapter. Pittayanon et al assessed prognostic factors affecting 6 month survival in patients with malignancy related GI bleeding and treated with TC-325(220). They found that good performance stays, non-end stage cancer and receiving definitive haemostatic treatment are independent predictors of 6-month survival. In a future trial I would look mortality rate over a similair time period and through multivariate analysis assess if factors such as transfusion requirements following treatment with TC-325 have an impact.

- One issue with the registry design is it does not control who receives the treatment and there are no control groups. This is not as scientifically rigorous as a randomised control trial. It provides real world data but to implement treatment options into clinical practice more controlled study designs are required. Designing a GI bleed clinical study can be difficult however this has now been shown to be possible. Sung et al carried out a prospective multicentre study evaluating the efficacy and safety of TC-325 in peptic ulcer bleeding(227). Chen et al designed a small RCT comparing TC-325 versus standard of care haemostatic modalities for the treatment of malignancy related bleeding (216). Most recently Pittayanoon et al carried a multicentre randomised control trial comparing RC-325 versus standard endoscopic treatment modalities(212).

- A further limitation is that there is can be interobserver variation in the definition of treatment failuire. I did not standardise how we define this in the study. Pittayanon et al(212) overcome this by recruiting independent endoscopists to review photo's or videos to confirm treatment failuire of achieving haemostasis in malignancy related bleeding. I would adopt a similair approach for both successful and failed treatments in a future randomised control trial.

6.7 Summary of the chapter

In the study in this chapter the efficacy of TC-325 in helping achieve immediate haemostasis following an upper GI malignancy related bleed is demonstrated. Early detection of cancers such as oesophageal cancer is important in helping achieve curative endoscopic therapy. In those not detected there is a risk of progression to malignant disease where there are often associated complications such GI bleeding which can often be difficult to treat with conventional endoscopic modalities. Early detection such as the AI systems demonstrated in chapter 3 and chapter 4 are one of the potential ways to aid early detection, therefore prevent progression and associated complications described here in chapter 6. I demonstrate:

- TC-325 is effective in achieving immediate haemostasis in GI bleeds secondary to oesophageal malignancy.

- TC-325 is effective in achieving immediate haemostasis in upper GI bleeds secondary to malignancies of all causes.

- The use of TC-325 in upper GI malignancy related bleed is associated with significant improvement in transfusion requirements in the short term after index endoscopy following treatment.

- TC-325 treatment as a monotherapy has a higher immediate haemostasis rate and lower re-bleed rate in comparison to the combination therapy group. Monotherapy treatment was also associated with a significant improvement in transfusion requirements.

CHAPTER 7

DISCUSSION AND FUTURE WORK

CHAPTER 7 DISCUSSION AND FUTURE WORK

The chapters in this thesis present a suite of studies with the focus on novel early detection techniques for dysplasia and neoplasia in Barrett's oesophagus with the use of artificial intelligence. Early detection is key to curative endoscopic therapy which has been made possible with the new endoscopic tools in the armoury in the last two decades. With advances in endoscopic therapy for oesophageal cancer comes risks which includes GI bleeding. Two chapters focus on haemostasis of GI bleeding using the TC-325 haemostatic powder in cases of post endoscopic therapy bleeding in the oesophagus. Chapter 6 focuses on the use of the TC-325 haemostatic powder in cases of GI bleeding in advanced cases of oesophageal malignancy. This highlights the importance of early detection of these lesions which is where AI will play such an important role. Significant mortality rates are associated with these advanced tumours due to associated complications such as bleeding.

7.1 Study 1 - The natural history of low-grade dysplasia in Barrett's oesophagus and risk factors for progression to high grade dysplasia and oesophageal adenocarcinoma

I go into detail in the discussion section in Chapter 2 analysing the main results from this chapter. Here I will provide a summary overview and the potential implication and next steps from these results.

The study in this chapter sets the scene for showing the importance of early detection of dysplasia such that curative endoscopic therapy can be offered to patients. It sets the scene for the artificial intelligence work on early detection of dysplasia in Barrett's oesophagus in chapters 3 and 4. This chapter adds to an important and controversial debate which is how under/over diagnosed is LGD in BO and the optimal management strategy for LGD in BO.

This was a retrospective study from a single large volume Barrett's tertiary centre which included 147 patients with a diagnosis of LGD in BO. The results showed a clear variability in the diagnosis of LGD from referring centres. Only a third of all referred patients had true confirmed LGD following centralised review by two Barrett's histopathologists. A third of patients were down staged to no dysplasia/indefinite for dysplasia. 32% of patients were upstaged to HGD.

The results support a clear need for all histopathology of dysplastic BO including LGD should be reviewed centrally in a tertiary referral centre with agreement on the diagnosis from two different BO histopathologists. There is a clear variation in the diagnosis following review. This is an important initial step as it will determine the management strategy for these patients. A metanalysis of randomised controlled trials assessed the efficacy and safety of RFA versus endoscopic surveillance for LGD in BO. It showed that RFA for LGD in BO reduced the risk of progression to HGD. They also concluded given the uncertainty in the natural history and course of LGD and risk of oesophageal strictures following RFA careful weighed up consideration should be given to whether the patients are offered endoscopic therapy or surveyed(228).

Another group also looked at the proportion of prevalent HGD or OAC in patients referred with LGD in BO. This was published after the publication of our work and supports our findings. They found that 27% of patients referred with LGD in BO from community hospitals were upstaged to HGD or OAC following endoscopic assessment in a tertiary Barrett's centre. As a result of this they concluded that the true rate of progression of LGD may be overestimated(184).

In our study we also tried to assess for any risk factors that can potentially contribute to an increased risk of progression in patients with true and confirmed LGD. Risk stratification is important to help determine those patients that are more at risk and therefore would support discussions with patients with regards to endoscopic interventions. In a multivariate analysis nodularity in BO, multifocal LGD and the history of endoscopic therapy were significantly associated with progression risk. After adjusting for endoscopic therapy, patients with multifocal LGD had a 4 times higher risk of progression than patients with unifocal LGD.

These findings contribute important data with regards to what are the important factors to consider in patients when deciding to offer treatment and what potential risk factors can form part of a potential risk score to help support these decisions. There is wide variation in previous results with regards to risk factors for progression. A study found there were no risk factors for progression associated with LGD in BO. A retrospective study of 69 patients found that persistent LGD was an independent risk factor for progression to HGD/OAC, and a further study showed that the length of BO was associated with risk of progression(173)(178)(174).

Our study supports that there is varied histopathological variation in the interpretation of low-grade dysplasia in Barrett's oesophagus. Linking in with the main theme of the whole thesis on artificial intelligence, automation of this process either during endoscopic assessment or during analysis of histology slides can potentially play a major role in minimising this variation. Faghani et al developed a deep learning model that was able to predict the grade of dysplasia on histology slides. The sensitivity and specificity for LGD was 81.3% and 100% respectively(229). However, before even getting to the stage of automation on histology slides, it will be key to try and be able to detect low grade dysplasia in Barrett's oesophagus real time during endoscopy. This something that has been reflected on during chapter 3 of this thesis.

Future work

This study sets the scene for a large multicentre study the aim of which would be to design a risk stratification tool to risk stratify patients with true LGD and determine whether endoscopic treatment is required or only surveillance is more appropriate for these patients.

The endoscopic data collected from this multicentre study can then be used to develop a deep learning model that can be used to differentiate LGD real time in endoscopy. This is often associated with subtle mucosal changes and will be more difficult to detect than HGD and OAC. Therefore, a lot more data would therefore be needed to develop a model which is able to robustly detect and then characterise this. A model can be developed to aid in the detection of LGD during pull through assessment in the oesophagus and then a further model to be able to classify the grade of dysplasia on magnification imaging.

7.2 Study 2 - The development of deep neural networks for the detection and localisation of dysplasia and neoplasia in Barrett's oesophagus and comparing the performance versus endoscopists

As far as I am aware the CNN developed and discussed in this chapter is the first one developed for the endoscopic detection and localisation of early cancer in Barrett's oesophagus using the Pentax endoscopic system. The CNN was trained, validated and tested using Pentax endoscopic data. There was a per image sensitivity and specificity of 91% and 79% respectively on i-scan 1 imaging. A segmentation model was trained to be able to localise an area of interest for biopsy with a sensitivity of up to 97%. The number of points of interests that can be generated can be tailored. There were two parts to the model – a classifier which detects the presence of dysplasia

on captured images during the pull through assessment in the oesophagus, followed by a segmentation model which helps localise an area of interest with a targeted biopsy or delineate an area of interest with a view to an endoscopic resection.

Every step taken in the development of the CNN's in this chapter considered what occurs in real world practice and mirrored those steps such that it can be developed further for use in the endoscopy unit. I summarise these steps here:

- A decision was made in the final model to test the ability of the CNN to detect dysplasia on still images. This mirrors the real-world practice where during a pull through assessment of the oesophagus the endoscopist takes still image of different segments of Barrett's oesophagus during this assessment. This is normally done after the oesophagus is cleaned. Therefore, to give the AI system a chance to give the most accurate diagnosis, predictions are made on still images.
- If there is an area of abnormality in the oesophagus this would often be assessed by the endoscopist on a still image where the pit pattern and vasculature can be carefully assessed. An AI prediction can be made at the same time. Therefore, using this kind of workflow using an AI system would not disrupt the real-world workflow.
- In a non-expert Barrett's centre, the aim of a Barrett's assessment is to assess for any areas of abnormality and take a biopsy. If there was dysplasia or cancer, then these cases are referred to a tertiary Barrett's centre for endoscopic resection. This was kept in mind when developing the CNN such that there is a minimal miss rate of early cancers. Therefore, as well as the classifier model, a segmentation model was developed which can localise the point of interest in the oesophagus where the biopsy should be targeted.

Importantly the results in this chapter showed that the AI system performed better than non-expert endoscopists. I decided to compare against non-experts as these are the cohort of endoscopists that would benefit from such an AI system. The sensitivity and specificity of the AI system for the detection of dysplasia on images was 96% and 88% respectively. The average sensitivity and specificity of 6 non expert endoscopists on the same images was 79% and 49% respectively.

Overall, the research into artificial intelligence and Barrett's oesophagus is very limited when compared to colonoscopies and polyp detection. Since our publication on an AI system for the

detection of dysplasia in i-scan 1 imaging there have been limited publications on the development Computer detection systems for Barrett's oesophagus(230).

Future work

The work in this chapter has formed the basis from which an AI system called CADU developed by Odin Vision has been formed. This is the first CE marked AI device for the detection of early cancer of Barrett's oesophagus in the world. It can now be used in the real time endoscopic setting and has the potential to have a positive impact on improving detection of early cancer in Barrett's oesophagus all over the world.

The next steps are currently in place for a prospective multicentre randomised trial to assess the AI system in real time in the endoscopy unit with a view to this potentially being used internationally in endoscopy rooms. This will potentially be the additional adjunct needed to reduce those miss rates of early cancer in Barrett's oesophagus. It will be like having an expert in the room supporting fellows, nurse endoscopists and consultants assessing an area of Barrett's in both district general and teaching hospitals.

7.3 Study 3 – The development of deep neural networks for the characterisation of dysplasia in Barrett's oesophagus on magnification imaging

To the best of my knowledge, this was only the second study assessing a CADx system for the characterisation of BO on magnification imaging. This was the first study of its kind using the Pentax imaging system.

The work in this chapter was a multicentre study from four European centres. The CNN was able to characterise dysplasia on magnification chromoendoscopic imaging with a sensitivity and specificity of 94% and 86% respectively on 350 high quality i-scan 3/OE images, a sensitivity and specificity of 92% and 84% respectively on 11,471 frame sequences and a sensitivity and specificity of 92% and 82% respectively on all the available 49,726 magnification i-scan 3 frames.

Like the steps taken in the AI experiments in chapter 3, real world methodology was always kept in mind. I kept in mind the fact that future steps will involve testing this in the endoscopy unit.

Therefore, it was important to replicate the real-world flow to make it a usable system. The main steps taken to maintain this include:

- When an endoscopist assesses Barrett's on magnification imaging this is often done using chromoendoscopy. Therefore, the testing set in these experiments were all i-scan 3 and optical enhancement magnification images. The CNN performed well on this in all the experiments. This is an important step before using this system in real time in clinical trials.
- Dataset was included from four different countries. This is to provide variability and generalisability to the data set. The long-term aim would be for such a system to be used in different centres and therefore it was important for the training data set to reflect this.
- The CNN was tested on three iterations of training sets to reflect different scenarios an endoscopist makes an assessment on magnification imaging and to ensure it performs well in all these scenarios. The CNN was tested on 350 high quality magnification images, which reflects the real-world scenario where an endoscopist makes an assessment then freezes the frame to assess the vascular and pit pattern to make a diagnosis. This would be the same point the AI system can then make a prediction without interrupting the endoscopists workflow.

The important thing to note is that it is important when developing a CNN like this to think about causing minimal interruption to an endoscopists workflow. Usability is important and minimal interruption means that it will more likely be used. This is what I tried to always keep in mind in both chapters 3 and 4 with the development process for these AI models.

The CADx model developed in this chapter links in well with the CADe model in chapter 3. I felt it was an important extension of CADe that had to be developed. The issue with magnification imaging is that is widely available in all units however it is underutilised. The main issue being unable to interpret magnification imaging. Interestingly it is an easier model to develop than a CADe system as the vascular and pit patterns are clearer and the images are often of a higher quality. One can therefore develop a CADx system which can match the level of an expert. Therefore, this process can be automated for non-expert endoscopists who would therefore not have to go through the difficulty of interpreting the significance or meaning of an image. The importance of the CADx is to confirm a diagnosis of dysplasia in an area of

abnormality detected by the CADe system. It is also very helpful for experts in delineating the resection margins to ensure an R0 resection.

As Jong et al discussed in their review paper of AI and Barrett's oesophagus. A CADx system has an important role in refining the diagnostic accuracy of a CADe system in the diagnosis of neoplasia in Barrett's oesophagus(117).

Future work

The foundations have now been laid for this to be tested in a multicentre prospective clinical study in the endoscopy unit.

As a start these CNN's can be used to differentiate dysplasia versus no dysplasia on magnification imaging. With the collection of larger volumes of data, the next step will be the development of a model which provides histological differentiation in real time between low grade dysplasia versus high grade dysplasia versus intramucosal adenocarcinoma. This will not differentiate next steps of management which is why we did not develop a specific model for this currently. If there is a lesion that management will always be an EMR regardless of the histological stage.

I think what the histological differentiation will be helpful in and what I think will be an important part of the pipeline for further development of an AI system for Barrett's oesophagus is predicting the depth of invasion. An endoscopic assessment can help determine whether a borderline resectable lesion based on imaging is endoscopically resectable during an assessment. An AI system which can predict the depth of invasion can help support an endoscopists prediction. The decision would be whether to proceed with an ESD/EMR or does the patient need to be referred early for surgery/oncological treatment.

7.4 Study 4 – Use of TC-325 for the management of bleeding following endoscopic therapy in the oesophagus

Adjuncts for endoscopists like those described in chapters 3 and 4 will be very important in supporting an early diagnosis for cancer in Barrett's oesophagus such that curative endoscopic therapy can be offered to patients. With advances in endoscopic treatment options there will be

risks associated with this including bleeding. It will be important to have clear management approaches for dealing with this at the time of endoscopy.

In chapter 4 we assessed the success of endoscopic haemostasis in patients with uncontrolled intraprocedural bleeding following endoscopic therapy in the oesophagus and compared that to outcomes in the rest of the upper GI tract.

This data was collected as part of the international TC-325 registry for GI bleeding. To the best of my knowledge at the time of publishing the work in that chapter this was the largest registry of its kind in the world.

Looking at outcomes in 40 patients with intraprocedural bleeding following endoscopic therapy in the oesophagus. There was a 100% haemostasis rate, one 30-day rebleed and no 30-day mortalities following treatment with TC-325. Treatment with TC-325 was effective as a monotherapy, as part of a combination therapy and as a rescue therapy treatment. The only re-bleed was in the combination therapy treatment in the patient that had an oesophageal EMR.

I propose an algorithm for how this haemostatic powder can be used within the GI bleed algorithm. One must keep in mind that once used it would be difficult to complete the endoscopic therapy in the same setting. It is better used at the end of the procedure. If used in the middle of a procedure, then further endoscopic treatment in the oesophagus may have to be completed in another endoscopic session. In the middle of a procedure, it would be better to use coagulation and/or adrenaline therapy so that the resection can continue to be completed in the same session.

Future work

There is now a need for a randomised control trial to help more clearly define the role for TC-325 in this cohort of patients within the GI bleed algorithm.

Setting up a randomised GI bleed study can be difficult and in the setting of intraprocedural oesophageal bleeding would be limited to specific tertiary centres therefore the patient's numbers would be small. Therefore, on the back of this work, I am currently leading an international consensus statement for haemostatic powders in collaboration with experts representing different parts of the world. This would make it a truly global statement. I am currently using the UCLA

RAND process to combine best available evidence with expert experiences. This will hopefully provide important guidance.

Another important study which is needed is comparing the different haemostatic powders and gels against each other in the setting of a randomised control trial.

7.5 Study 5 – Use of TC-325 for the management of upper gastrointestinal bleeding secondary to oesophageal cancer

AI as described in chapters 3 and 4 will help support endoscopists with the detection of early cancer in Barrett's oesophagus. Despite advances in chromoendoscopy and endoscopic imaging techniques there is still a significant miss rate. Dhaliwal et al analysed data from 1066 patients and found a missed dysplasia rate of 13%(231). A statistical modelling study estimated the frequency of missed Barrett's oesophagus during surveillance endoscopies to be approximately 50%(232). AI will help bridge this gap. If these cancers are not detected early there can be several complications associated with advanced oesophageal malignancy including GI bleeding.

Chapter 6 assesses the outcomes of the use of TC-325 for the treatment of Oesophageal malignancy related bleeding. It also compares the outcomes of treatment of oesophageal malignancy versus gastric/duodenal malignancy bleeds.

There was an immediate haemostasis rate of 93% following treatment of oesophageal cancer related bleeding with a 30-day re-bleed rate of 17%- and 7-day mortality of 8%. 30-day mortality was 36% and was double the gastric malignancy bleed cohort (15%). This is explained by the poor underlying prognosis associated with advanced oesophageal malignancy. This was also a high-risk cohort of patients as reflected by the median Rockall score of 8. Therefore, the most likely cause of mortality was the poor prognosis of the underlying diagnosis and co-morbidities.

An important finding from this work was that there was an overall improvement in transfusion requirements in all malignancy related bleeds following treatment with TC-325. This effect remained when TC-325 was used as a monotherapy.

Since the publication of my work and doing the experiment in thesis there has been published randomised control trials. Martins et al randomised 62 patients with malignancy related bleeding

to receive either TC-325 or be part of a control group where endoscopic treatment is not mandatory. They found TC-325 was effective in achieving immediate haemostasis but they found that it did not reduce 30-day mortality, 30-day re-bleeding, blood transfusion or length of hospital stay(233). Pittayanon et al published a randomised control trial of 106 patients which showed that TC-325 allowed for greater immediate haemostasis rates and lower 30-day rebleeding rates versus standard endoscopic modalities for the management for malignancy related GI bleeding(212).

Future work

There is now growing evidence that TC-325 is effective for the immediate management of a malignancy related GI bleed. There is a clear need to gain international consensus and better define its role within the GI bleed algorithm to help guide clinicians with regards to when it can be appropriately used. I think there is conclusive evidence that it can be an effective first line monotherapy treatment which can provide an effective bridge towards definitive surgery or radiotherapy.

Currently I am leading on an international consensus statement to help better define the role of haemostatic powders like TC-325 within the GI bleed algorithm. This will combine best practice based on expert opinions as well as best available evidence using the RAND UCLA methodology. This will be published in the coming months and will hopefully be the first international consensus statement of its kind.

7.6 Overall conclusions

The suite of studies in this thesis advances our knowledge on potential novel early detection techniques of cancer in Barrett's oesophagus real time during endoscopy. Chapter 2 provides the basis of understanding of the variability in the diagnosis of low-grade dysplasia in non-expert centres. Chapters 3 shows the step wise development of a novel AI systems for the detection of dysplasia in Barrett's oesophagus including low grade dysplasia. This provides a solution for the problems highlighted in chapter 2. The performance of the AI system outperformed non expert endoscopists. This chapter has provided the platform for the work that has contributed to the development of the first CE marked AI device for dysplasia detection in BO in the world. Chapter 4 shows the development of an AI system which will support the AI system developed in chapter 4 as part of a two-stage system by characterising dysplasia on magnification imaging. The added

benefits of the AI system in this chapter are it will support experts to utilise magnification imaging more by automating the process of diagnosis. It will also be particularly useful to experts in delineating resections and achieving clear (R0) resections.

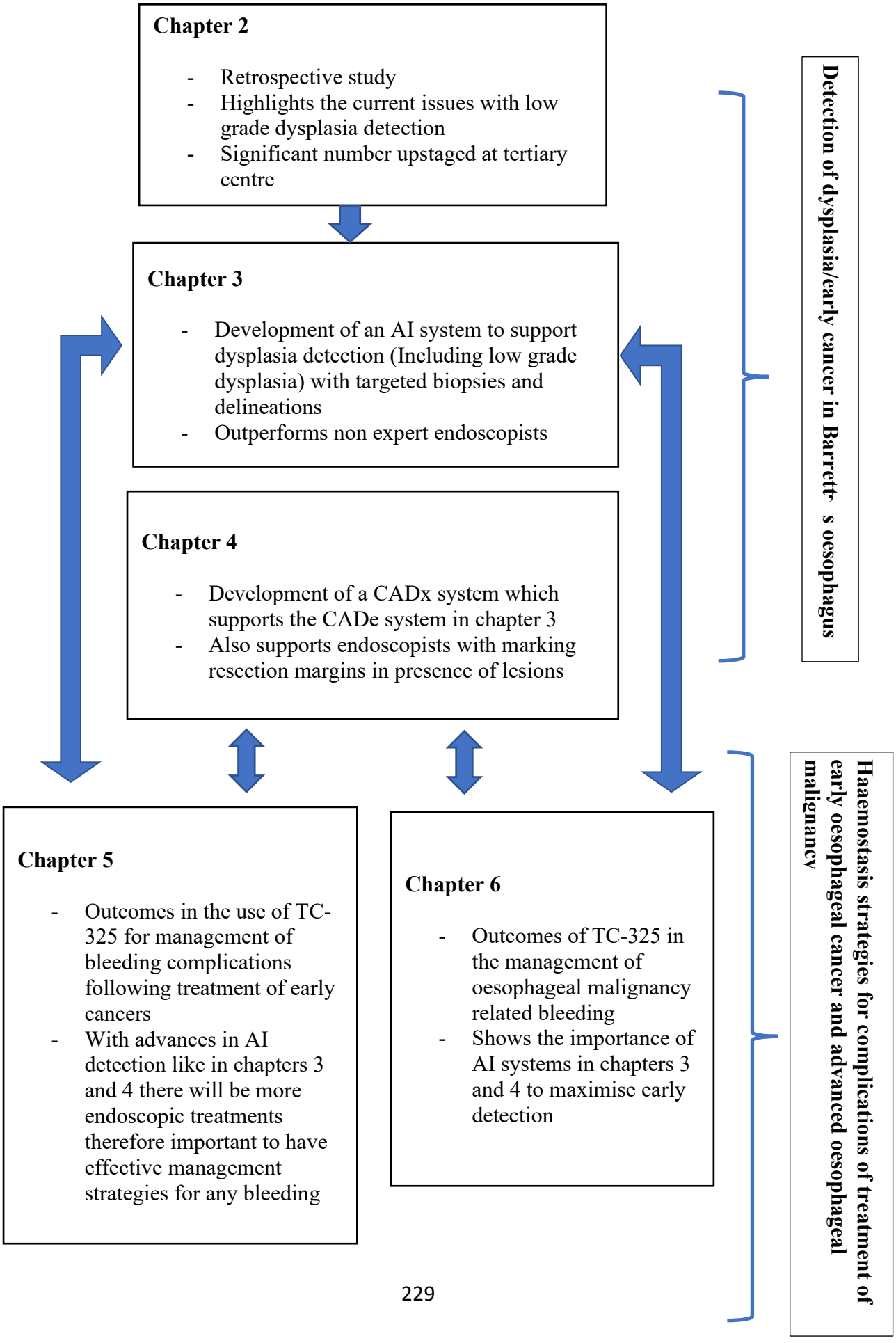
Chapters 5 and 6 provide important findings which support chapters 2,3 and 4. With the detection of early cancer curative endoscopic therapy is offered. There can be associated complications of bleeding, and it is important to understand the best management strategy. In chapter 5 I present outcomes of the use TC-325 in the management of intraprocedural bleeding in a multicentre study. I try and define a clear role for this in the GI bleed algorithm. This is the largest number of cases of its kind published in the world at the time of publishing the work in that chapter.

Chapter 6 provides an important insight in the potential risks of undetected oesophageal progressive malignancy and the potential risks of bleeding. It reflects the importance of AI to prevent these complications with earlier detection. Here I show the other outcomes from the use of TC-325 in oesophageal malignancy related bleeding. I also show the positive impact it can potentially have on transfusion requirements which is particularly important in palliative patients to minimise hospital admissions.

In the management of patients with dysplasia in Barrett's oesophagus we need to keep in mind a global focus of early detection strategies as well as treatment strategies including ways of minimising any complications which is what I have done in the suite of studies in this thesis all of which have been published in peer-reviewed journals.

Figure 44 brings together a conclusive link to all the chapters in thesis where I have answered some important questions which overall will potentially have an important impact on patient care.

Figure 44: Algorithms showing the link between all the thesis chapters



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APPENDIX

Appendix 1

Instruction sheet (Barrett's oesophagus detection on images)

- You will scroll through a selection of random images from different patients. This includes images with no evidence of dysplasia in Barrett's oesophagus and images with dysplasia/early cancer in Barrett's oesophagus.

- If there is no evidence of dysplasia scroll to the right onto the next image

- If there is evidence of dysplasia place a dot on where you will be confident in obtaining dysplastic tissue with a targeted biopsy

- To generate a dot on the right-hand side of the screen under 'create shape' switch from 'box' to 'points' then click on create shape. Place your dot on the dysplastic area. Then press 'Stop creation'. Then click right and proceed to the next image.

- On completion of all the images 'open menu' on the bottom left hand of the screen then 'save work'.

- You can try out the test image before starting the experiment

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CHAPTER 2

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Data analysis: MH, JGP, DL
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Manuscript revision: All authors
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   Journal of Gastroenterology and Hepatology

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Each author contributed to the design of the manuscript; each author was involved in the literature review, drafting, revision, editing and final approval of the final version of the manuscript.

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